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(71) Applicant (for all designated States except US):		A/S DUMEX (DUMEX LTD) [DK/DK]; 11 Dalslandsgade, P.O. Box 1736, DK-2300 Copenhagen S (DK).		
(72) Inventors; and				
(75) Inventors/Applicants (for US only):		DYRSTING, Hjarne [DK/DK]; Geelkovvej 17, DK-2830 Virum (DK). KOCH, Torben [DK/DK]; Roedkildevej 62, DK-2400 Copenhagen (DK). PETERSEN, Kim, Voulund [DK/DK]; Rosenlund 35, DK-2635 Vallensbæk (DK).		
(74) Agents:		COCKBAIN, Julian et al.; Frank B. Dehn & Co., Imperial House, 15-19 Kingsway, London WC2B 6UZ (GB).		
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(54) Title: DRUG SALTS

(57) Abstract

It has been found that sugar acid salts represent beneficial controlled release forms for basic organic drug compounds. Examples of appropriate salts include mono, di, oligo and polysaccharide poly-O-sulphonic acid salts of antibiotics such as tetracyclines.

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Drug Salts

This invention relates to salts of biologically active organic molecules (drugs) with sugar acids, in particular salts with mono-, di- and oligosaccharide poly-O-sulphonic and poly-O-phosphonic acids.

It is common practice in the pharmaceutical industry to use salt forms of drugs, e.g. salts with physiologically acceptable organic or inorganic acids and bases, such as hydrogen chloride, sulphuric acid, maleic acid, ethanolamine, meglumine and the like. For drugs with basic groups, e.g. amine groups, it is feasible to use salts with organic or inorganic acids.

The drug salts are frequently used in preference to the drug itself, for example because of their higher solubility or greater biotolerability.

Many alkaline drug compounds cause irritation of tissue or mucosa. In particular, high local concentration can cause severe irritation and ulceration of the oesophagus. These compounds may also have an unpleasant taste and accordingly they can be administered provided with a polymeric film coating to delay drug release. Such coatings however add to the cost and complexity of formulation.

The present invention is based upon the finding that drug salts with sugar acids exhibit surprising beneficial properties, in particular enhanced uptake and controlled release properties. In particular, insoluble or poorly soluble drug:sugar acid salts have been found to have a drug release profile which is not undesirably dependent on the pH of the surrounding body fluid, e.g. gastrointestinal fluid.

In our earlier patent application, PCT/DK94/00341, the aminoglycoside salts of one sugar acid, sucrose-octa-O-sulphonic acid (SOS), were

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described as having beneficial properties, especially for oral treatment of H. pylori related stomach and duodenal ulcers. We have now found that in general the poorly soluble or insoluble salts of water soluble sugar acids with organic drug compounds (as opposed to soluble drug:sugar acid complexes or complexes of organic drugs with insoluble sugar acid resins) also exhibit beneficial properties.

By the term "sugar acids" is meant herein carbohydrates, e.g. cyclitols (such as inositol) or mono-, di-, oligo- and poly-saccharides (such as xylose, fructose, glucose, sucrose, lactose, maltose, cellobiose, trehalose, sorbitol, mannitol and dextran) which carry sulphur or phosphorus oxyacid groups on the carbohydrate (e.g. saccharide) moieties (e.g. esters of oxyacids, such as phosphorus and sulphur oxyacids, with the sugar hydroxyls), which sugar acids, in the case of the polysaccharides (and preferably also the oligosaccharides, disaccharides, monosaccharides and cyclitols), contain a high ratio of acid groups to monosaccharide units, i.e. at least 2:1, preferably at least 3:1. Such sugar acids have been used in various medicaments but, other than in our copending application PCT/DK94/00341, have not previously been proposed for use in forming salts, rather than soluble complexes, with organic drug compounds.

Thus viewed from one aspect the invention provides a therapeutic compound being sugar acid salt of a biologically active organic molecule other than an aminoglycoside:SOS salt, preferably the salt with a polybasic sugar acid, especially a mono or disaccharide poly-O-sulphonic acid.

The sugar acid used according to the invention is preferably a sulphate or phosphonate ester, particularly a sulphate, of a mono-, di- or trisaccharide, in particular a polyester or perester, i.e. a compound in which more than one and optionally all of the sugar

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hydroxyls are esterified, preferably a compound carrying at least 2, and especially at least 3 oxy-acid groups per saccharide unit.

The disaccharide sulphonic acids are especially preferred, in particular the sucrose sulphonic acids such as sucrose-octa-O-sulphonic acid (SOS). Monosaccharide polysulphonic or poly-O-phosphonic acids, such as phytic acid, are also preferred.

The drug may be any organic drug compound capable of forming a sugar acid salt, in particular a compound containing an electron donor base group such as a basic nitrogen atom, e.g. an amine, imine or ring nitrogen. The drug compounds preferably contain one or more exposed protonatable amine functionalities, particularly preferably a plurality of such groups. Drug compounds useful in the production of the poorly water soluble drug:sugar acid salts of the invention include antibacterial agents (in particular tetracyclines, aminoglycosides, glycopeptides, polypeptides and macrolides), antiviral agents, antimycotics, anti-amoebics, anti-allergics (such as antihistamines), analgesics, anxiolytics, sedatives, hypnotics, anti-emetics, anti-migraine agents, anti-motion sickness agents, antidepressants particularly tricyclic antidepressants (such as imipramine, amitriptyline and doxepin), alkaloids, cardioprotective agents (such as calcium antagonists, e.g. diltiazem, and azepine derivatives), adrenergics, anticholinergics, antispasmodics, antianorexics, and muscle relaxants, particularly the tricyclic muscle relaxants (e.g. cyclobenzaprine and benzoctamine).

The drug sugar acid salt particularly preferably has a low water solubility, for example less than 10g/L, preferably less than 1g/L more preferably less than 10^{-2} mM/L, in deionized water at ambient temperature. This poor water solubility both imparts favourable biorelease characteristics and facilitates preparation

of the salts by precipitation from aqueous solution.

The drug compound may be, and preferably is, polybasic and the sugar acid, as mentioned above, is preferably a poly or perester which is thus also polybasic. Accordingly the drug salt of the invention may contain further physiologically tolerable counterions. In this regard alkali and alkaline earth metal (e.g. sodium, potassium, magnesium and calcium), aluminium and ammonium and counterions derived from organic bases such as ethanolamine, diethanolamine and meglumine are preferred cations, while bromide, chloride, sulphate, maleate, acetate, fumarate, succinate and other physiologically tolerable anions derived from inorganic or organic acids are preferred anions.

In the solid state, the drug salts of the invention are amorphous or crystalline materials, e.g. presented in sterile, for example sterile crystalline, form.

The drug salts of the invention may be formulated together with conventional pharmaceutical carriers or excipients, optionally together with further bioactive agents, in conventional pharmaceutical administration forms, e.g. powders, capsules, tablets, coated tablets, suspensions, dispersions, drops, aerosols, suppositories, plasters, pastes, creams, emulsions, etc. These may be in sterile form.

Accordingly, viewed from a further aspect the invention provides a pharmaceutical composition comprising a biologically active organic compound in the form of a salt with a sugar acid, together with at least one physiologically acceptable carrier or excipient.

Viewed from a yet further aspect the invention also provides a method of treatment of a warm-blooded animal, e.g. a human or a non-human mammal, with an effective amount of a biologically active organic compound to combat a condition responsive to said compound, said method comprising administering to said warm-blooded

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animal an effective amount of said organic compound in the form of a salt with a sugar acid.

Viewed from a further aspect, the invention also provides a sugar acid salt of a biologically active organic molecule, other than an aminoglycoside:SOS salt, for use as a therapeutic agent.

Viewed from another aspect the invention also provides the use of a sugar acid salt of a biologically active organic molecule, other than an aminoglycoside:SOS salt, for the manufacture of a medicament for use in combatting conditions responsive to said organic molecule.

Sugar acids are produced by esterification of a mono-, di-, oligo- or poly-saccharide with a polybasic sulphur or phosphorus oxyacid (e.g. a phosphorous or phosphoric acid or a sulphur oxyacid such as sulphurous or more preferably sulphuric acid) or an activated analog thereof (such as sulphur trioxide). One or more, and preferably most or all of the sugar's hydroxyl groups are esterified to yield oxygen-attached acid groups such as O-sulphonic acid groups.

The sugar acid conveniently has a molecular weight of up to 1000kD. Preferably however the molecular weight is below 150kD, and especially below 30kD. Mono-, di- and oligosaccharides having up to 100, particularly no more than 8, especially 1, 2 or 3, monosaccharide units are particularly preferred.

The sugar acids are known compounds and are discussed for example by Ochi et al in *Chem Pharm Bull* 28:638-641(1980) and WO89/07932 (Niels Bukh A/S).

Preferred among the sugar acids useful according to the present invention is the sulphate octa-ester of sucrose, β -D-fructofuranosyl- α -D-glucopyranoside octakis (hydrogen sulphate), hereinafter referred to as sucrose-octa-O-sulphonic acid or SOS.

SOS may be prepared by sulphating sucrose with sulphur trioxide in pyridine. SOS forms crystalline,

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water soluble sodium, potassium, caesium, rubidium and ammonium salts as reported by Ochi (supra).

SOS also forms an aluminium salt, $C_{12} H_{54} Al_{16} O_{75} S_8$, which is known as sucralfate. This aluminium salt may be prepared by reaction of SOS with aluminium hydroxide (see US-A-3432489 (Chugai)) and is widely used for the treatment of gastric ulcers, its effectiveness being ascribed to the aluminium hydroxide ions which act as acid neutralizers and absorb pepsin and bile salts (see Nagashima in Clin. Gastroenterol 3 (Suppl. 2):117-227 (1981)).

The use of soluble complexes of certain sugar acids has been proposed in the literature. Thus Koh et al. in US-A-3506642 proposed the use of organic base complexes with heparinic acid as orally active heparinoid complexes, e.g. for use as anticoagulants, and Yoshikawa et al. in J. Pharm Dyn 5: S-69 (1982) proposed the use of macromolecular complexes of bleomycin with dextran sulphate to promote lymphatic bleomycin uptake. By contrast Mihai et al. in Cellulose Chem. Technol. 27: 393-403 (1993) proposed loading insoluble particulate polysaccharide cation exchangers with propranolol to provide a sustained release administration vehicle for propranolol.

The present invention however is concerned not with soluble drug:sugar acid complexes or with insoluble ion-exchange particles loaded with drug molecules, but with the insoluble or poorly soluble salts which organic drug compounds can form with soluble sugar acids.

Although no medical uses for sugar acid salts with bioactive organic counterions have been proposed, there have been several suggestions for the coadministration of sugar acids or their metal salts together with bioactive agents. Thus for example WO89/07932 (Niels Bukh A/S) describes sugar acid metal salts as ingredients for a topical preparation for periodontal treatment, EP-A-403048 (Warner Lambert) discloses admixtures of

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sucralfate with other anti-ulcer agents, and WO92/18143 (Smith Kline Beecham Plc) discloses admixtures of sucralfate with various antibiotics.

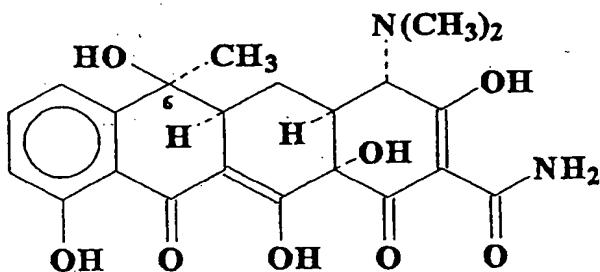
The drug salts of the invention are generally suited for use where controlled release of the active drug is desired, e.g. for topical administration especially to mucous membranes or administration, preferably per oral, into the gastrointestinal tract.

A particularly valuable characteristic of the salts according to the invention is their ability to release the drug when placed in an ion containing aqueous environment such as gastrointestinal fluid, essentially it appears as a result of ion exchange with competing cations such as sodium or magnesium that are present in the body fluid.

One particularly suitable group of drug compounds for use according to the invention are the antibiotics, in particular basic nitrogen atom containing antibiotics, such as aminoglycosides, tetracyclines, polypeptides, macrolides and glycopeptides.

One preferred group of antibiotic drugs with which to form the sugar acid drug salts of the invention is the tetracyclin antibiotics, a preferred example being doxycyclin.

For more than 50 years tetracyclines have been used as antibiotics. By the term "tetracyclin" is meant an antibiotic of the class containing the fused tetracyclic ring system of tetracyclin itself:



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The tetracyclins belong to a group of antibiotics which are manufactured by fermentation of various Streptomyces species. The most widely used are doxycyclin, oxytetracyclin, chlorotetracyclin and tetracyclin. A number of semisynthetic tetracyclins are known, for instance metacyclin and minocyclin. The most widely used of these semisynthetic tetracyclins is α -6-deoxy-5-hydroxy-tetracyclin (doxycyclin). This broad-spectrum antibiotic was first synthesised in 1962 and is marketed by Pfizer under the name Vibramycin®.

Doxycyclin is available in several different forms: doxycyclin monohydrate, doxycyclin hydrochloride (hyclate), doxycyclin carageenate, doxycyclin calcium and doxycyclin phosphate (fosfate).

Doxycyclin has a mode of action which is common with other tetracyclins, namely inhibition of bacterial protein synthesis. This arises through inhibition of the binding of aminoacyl-tRNA primarily to 70S ribosomes but also to 30S ribosomes. This results in a bacteriostatic effect. Tetracyclins are active against a broad range of both gram positive and gram negative bacteria, aerobes as well as anaerobes.

Bacterial resistance to tetracyclins is common both in vitro and in vivo, and the resistance is transferred by a plasmid. Due to the bacteriostatic effect of the tetracyclins they usually can not be combined with other cell-cycle specific antimicrobial agents, as the resting cells do not change cell cycle.

Most tetracyclins are incompletely absorbed and their absorption is dependent on the concomitant food intake. Absorption of doxycyclin however is almost complete (73-95%) and independent of food intake (see Saiven et al. in Clin. Pharmacokinetics 15:355-366 (1988)).

The pharmacokinetic parameters of the different salts (hyclate, monohydrate, carageenate etc.) of doxycyclin do not significantly differ under standard

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conditions (see Saivin et al. (supra) and Grahnén "Effect of increasing gastric pH on the relative bioavailability of doxycyclin carageenate tablets 100mg (Kabi Pharmacia) in comparison", Internal Study Report, PCB, Sweden, (1991)).

Two factors have been reported which influence the pharmacokinetics of doxycyclin. The pH in the stomach (see Grahnén (supra)) and the concomitant administration of oral antacids (see Nguyen in *Antimicrob. Agents Chemother.* 33:434-436 (1989)).

An increased pH of the stomach (see Bogardus et al. in *J. Pharm Sci* 68:1183-1184 (1979)) decreases the bioavailability of doxycyclin monohydrate whereas dissociation and absorption of doxycyclin hyclate and doxycyclin carageenate are independent of pH.

The increased pH in the stomach after omeprazole administration is thus expected to slow down the dissolution of doxycyclin monohydrate and thereby decrease its absorption.

Doxycyclin was first introduced into clinical practice in 1968 as the hydrochloride salt, doxycyclin hyclate. This salt was formulated in tablets or capsules. However, it was soon shown that these formulations had serious side effects. In a study of adverse drug reactions from antibiotics, 35/113 (31%) of patients treated with doxycyclin hyclate after questioning reported nausea and vomiting while 24/373 (6.4%) spontaneously reported nausea and vomiting. These frequencies were 3-fold higher than those reported with other antibiotics.

Another side effect of doxycyclin hyclate is oesophageal ulceration, which can occur if the capsules for some reason do not reach the stomach but remain in the oesophagus.

A solution to these problems has been attempted by the introduction of doxycyclin hydrate (base). This new formulation eliminated the above mentioned side effects,

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but it soon became apparent that the bioavailability in a number of patients, which were also in treatment with antacids and the like, was significantly reduced. This can be explained by the lack of acid production in the stomach being the cause of reduced dissolution of doxycyclin hydrate.

Considering that a great deal of the population has elevated gastric pH caused by either achlorhydria or due to the intake of antacids, H₂-blockers, omeprazole or the like, antibiotic treatment with doxycyclin hydrate gives an unacceptably low bioavailability.

One solution to this problem has recently been suggested by the introduction of doxycyclin carrageenate, which has a satisfactory bioavailability in subjects with elevated gastric pH. In subjects with normal pH conditions in the stomach, the use of doxycyclin carrageenate has no advantage due to the spontaneous cleavage of doxycyclin carrageenate into doxycyclin H⁺ and carrageenate ion.

By using different pharmaceutical preparations of doxycyclin, attempts have been made to achieve a controlled release effect.

One solution has been the use of film coated tablets. A coated doxycyclin hydrate formulation was developed which showed less tendency to disintegrate in the oesophagus (see Delphre et al. in *Digestive Disease and Sciences* 34:197-800(1989)). An enteric coated pellet formulation of doxycyclin (sold under the names Doryx® and Doxylets®) has been developed to prevent the total dose of doxycyclin hydrate dissolving in a small area of the stomach. Such formulations have been shown to have a reduced (approximately 50% reduction) rate of nausea and vomiting and an unchanged bioavailability. A pellet formulation however does not automatically have an unchanged bioavailability. In a doxycyclin pellet formulation developed at the university of Nanking, China, it was found that 200mg of the pellet formulation

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were bioequivalent to 100mg of the standard doxycyclin hydiate formulation (see Qiu et al. in *Acta Pharm. Sinica* 21:370-376 (1986)). Therefore a need still exists for tetracyclin and particularly doxycyclin formulations with controlled release properties.

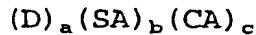
In EP-A-91409 (Kabi Vitrum) complexes between carrageenan and three drug compounds are described. Carrageenan is a sulphated polysaccharide with a molecular weight from 100kD to 1000kD which carries a low density of sulphate groups per saccharide unit. Complexes of Aubygum x2 (a mixture of kappa and lambda carrageenans) with doxycyclin, emepronium and propranolol were disclosed. The doxycyclin complex is insoluble in water, but in the gastric juice doxycyclin is released at the same rate as from the soluble doxycyclin hydiate. The drug release profile however is strongly pH dependent.

The sulfosalicylate of doxycyclin is known from GB-A-1305860 (Alfa Farmaceutici). This salt is sparingly soluble in water and is used in the doxycyclin manufacturing process. The sulfo-salicylic acid salt however has no clinical use, as sulfosalicylic acid is not accepted for medicinal use.

It has now surprisingly been shown that tetracyclines form sparingly soluble salts with sugar acids, salts which can be used for the controlled release of the tetracyclin antibiotic within the gastrointestinal tract.

The salts with SOS are crystalline and particularly preferred.

The drug:sugar acid salts of the invention may be described by the general formula



where D, SA and CA respectively represent the drug molecule (or a cation thereof), the sugar acid (or an

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anion thereof) and a physiologically tolerable counterion, a and b are positive numbers (not necessarily integers), and c is zero or a positive number.

Thus, by way of example, the tetracyclin:SOS-salts can be described by the following formula:



wherein TC is a tetracyclin molecule, and x is a number of from 0 to 20 indicating the amount of water which forms a hydrate with the new salt or which is physically bound to the new salt.

A further exemplary group of the drug compounds which can be presented according to the invention as their sugar acid salts are the amino glycosides.

Examples of suitable aminoglycosides include amikacin, apramycin, arbekacin, bambermycins, butirosin, dibekacin, dihydrostreptomycin, fortimycin, gentamicin, isepamicin, kanamycin, micronimycin, neomycin, netilmicin, paromycin, ribostamycin, sisomicin, streptomycin and tobramycin. Amikacin, gentamicin, kanamycin, neomycin, streptomycin and tobramycin are particularly preferred.

The aminoglycoside:sugar acid salts are particularly suitable for use in the treatment of ulcers, especially stomach or duodenal ulcers and particularly ulceration associated with Helicobacter pylori.

Helicobacter pylori (previously known as Campylobacter pylori) is a helical Gram-negative organism which is present in the stomach mucosa. Many recent tests have shown a clear correlation between the presence of H. pylori in the stomach mucosa and histologically demonstrated gastritis. This seems to indicate that this organism is wholly or partially responsible for the development of gastritis with

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ensuing ulcerations (see Scand. J. Gastroenterol. (1988) 23 suppl. 142, pages 93-100).

H. pylori is sensitive to a number of known antimicrobial substances in vitro. Furthermore, several publications disclose that the treatment of gastritis with antimicrobial agents, such as β -lactams (e.g. amoxicillin) or bismuth salts can result in the eradication of H. pylori in vivo (see Antimicrobial Agents and Chemother. 1993, pages 1184-86).

The traditional treatment of ulceration in the human stomach or the duodenum involves administering acid neutralising agents or anti-histamines of the H₂-inhibitor type (e.g. ranitidine, cimetidine, etc.) which reduce the production of acid, and acid pump-inhibitors, such as omeprazole. This treatment as such is efficient, but it has a short-term effect only as, in almost every case, there is a relapse due to H. pylori infection still being present.

Today the optimum treatment of ulceration caused by H. pylori involves combined administration of bismuth subcitrate, amoxicillin and metronidazole. This treatment cures 60-90% of the patients (see Ann. Rev. Med. 1992 (43) page 142).

However, there are certain side effects associated with this therapy: bismuth subcitrate may cause constipation and in large doses it may be neurotoxic; and amoxicillin and metronidazole are systemically acting antibiotics which may cause development of allergy or resistance and influence the microflora in the colon.

Therefore, there is a continuing need for a preparation for local treatment of H. pylori infection in the stomach and the duodenum.

Amino glycosides are a group of antibiotics which have a good in vitro effect on H. pylori. The following MIC-values are known from the literature:

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TABLE 1

	Average MIC 90 range
AMIKACIN	0.5
GENTAMYCIN	0.04 - 1
KANAMYCIN	0.04 - 2
STREPTOMYCIN	0.04 - 1.28
TOBRAMYCIN	0.04 - 0.64

(see Antimicrobial Agents and Chemother., 1986, pp. 510-511, J. Antimicrobial Chemother. 1986, 17, pp. 309-314, and Scand. J. Gastroenterol., 1988, 23 (suppl. 142), pp. 93-100).

Thus far however amino glycosides have not been found to be suitable for use in the treatment of *H. pylori* infections because they are not absorbed following peroral administration of therapeutic doses. When readily soluble salts of amino glycosides are administered orally, they do not influence the stomach and duodenum mucosae due to their poor tissue penetration and thus are not capable of eradicating *H. pylori*. Instead they will have a considerable influence on the colon microflora and may cause diarrhoea. Amino glycosides could be administered parenterally in ulcer treatment but this is impractical as they have known oto- and nefro-toxic properties.

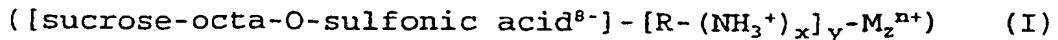
Amino glycosides belong to the group of sugars having a number of amino groups, preferably 4,5 or 6. They are obtained by fermentation of various Streptomyces- or Micromonospora-species. Due to the many hydrophilic hydroxy or amino groups in the amino glycosides they and the normally used pharmaceutical salts thereof are readily soluble in water.

As the amino glycosides and the sugar acids are generally polybasic it is not immediately predictable that they should together form low water solubility salts.

By way of example the aminoglycoside SOS salts can

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be represented by the formula



where $R(NH_2)_x$ is the aminoglycoside (preferably a mono-, di- or trisaccharide), M^{n+} is a pharmaceutically acceptable cation, preferably alkali metal, alkaline earth metal, aluminium or ammonium ions, x is an integer having a value of from 1 to 6, n is an integer having a value of from 1 to 3, z is zero or a positive number having a value of up to 4, y is a positive number having a value such that the product of y and x is from 4 to 8, and the sum of the product of x and y and the product of n and z is 8.

It has been found that it is possible to form well defined compounds between sucrose-octa-O-sulfonic acid and an amino glycoside and then to produce mixed salts by introducing cations. The following pharmaceutically acceptable cations are preferred: alkali metal ions, such as Na^+ and K^+ ; ammonium; alkaline earth metal ions, such as Ca^{2+} and Mg^{2+} ; and aluminium.

The novel drug:sugar acid salts according to the invention preferably have comparatively low solubility in water, such that when stirred into water they form oily or sticky gels with a high degree of affinity to the inside surface of the container. They will preferably also have this affinity for biological surfaces such as the mucosae of the stomach or the duodenum.

Furthermore, the novel salts will preferably release the drug compound in aqueous solutions at a low pH. Therefore, the aminoglycoside salts for example will be suitable for the treatment of ulceration in the stomach and the duodenum caused by H. pylori.

By peroral administration in a suitable pharmaceutical formulation, the novel aminoglycoside

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salts produce a gel which covers the mucosae of the stomach and/or the duodenum when the stomach pH is neutral or slightly below neutral.

Upon consumption of food, the stomach will secrete hydrochloric acid. H. pylori is sensitive to acid, such as gastric acid, but it has developed a protective measure. This protective measure consists of H. pylori producing an enzyme, urease, which splits urea into ammonia and CO₂. The ammonia thus formed neutralizes the gastric acid.

When the areas of the stomach which are infected with H. pylori come into contact with the aminoglycoside salts according to the invention, the ammonia formed causes release of the amino glycoside which subsequently kills the H. pylori.

If insufficient ammonia to neutralize the gastric acid is formed, the gastric acid will itself release the amino glycoside from the novel salts.

Other examples of amine group containing antibiotics which can be used to form poorly water soluble drug:sugar acid salts according to the invention include polypeptides (such as bacitracin and polymyxin), glycopeptides (such as vancomycin), and macrolides (such as erythromycin and oleandomycin), streptomycins and penicillins.

These poorly water soluble salts can again advantageously be used to achieve controlled release of the antibacterial agent within the gastrointestinal tract, e.g. following peroral administration.

The drugs usable in this fashion are not restricted to the antibiotics and indeed poorly water soluble salts can be produced with a wide range of acid salt forming drug compounds, for example neuroleptics, antidepressants, e.g. tricyclic antidepressants (such as imipramine), the structurally related tricyclic muscle relaxants (such as cyclobenzaprine), anticholinergics, antihistamines, antianorexics, cardioprotective azepine

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derivatives (such as benzothiazepinones like diltiazem), and alkaloids (such as the antitussive agent noscapine).

Further drug categories which may be considered include antivirals (such as acyclovir, idoxuridine and tromantadine), antimycotics (such as miconazole, ketoconazole, fluconazole, itaconazole, econazole, terconazole, and polyenes such as amphotericin B or nystatin), anti-amoebics (such as metronidazole and tinidazole), antihistamines (such as diphenylhydramine, chlorpromazine, pyrilamine and phenyltoloxamine), calcium agonists (such as verapamil and nifedipine), anxiolytics, sedatives and hypnotics (such as benzodiazepines, diazepam, nitrazepam, flurazepam, estazolam, flunitrazepam, triazolam, alprazolam, midazolam, temazepam, lormetazepam, brotizolam, clobazam, clonazepam, lorazepam and oxazepam), anti-migraine agents (such as sumatriptan), anti-motion sickness agents (such as cinnarizine), anti-emetics (such as ondansetron, tropisetron and granisetron), adrenergics (such as amphetamine), antispasmodics (such as aminopentamide, metixene and dicyclomine), ataractics (such as benactyzine), antihypertensives (such as hexamethonium and pentamethonium), analgesics and alkaloids (such as 2,6-diamino-3-phenyl-azopyridine, morphine, papaverine and ethaverine), antitussives (such as dihydrocodeine, phenylpropanolamine, guaiacol, cloperastine and dextromorphen), bronchodilators (such as dimethylephedrine), antipsychotics (such as imipramine), coronary dilators (such as etafenone), antiarrhythmics (such as procainamide), hypotensives (such as hydralazine and clonidine) and peripheral vasoconstrictors (such as tolazoline).

Further examples of amine containing drug compounds include acetophenazine, amitriptyline, brompheniramine, carbinoxamine, chlorcyclizine, cyclizine, desipramine, dexbrompheniramine, dexchlorpheniramine, ergotamine, nortriptyline, quinidine, benztropine, flunarizine,

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fluphenazine, hydroxychloroquine, hydroxyzine, meclizine, mesoridazine, methdilazine, methysergide, pheniramine, pyrilamine, tripeleannamine, triprolidine, promazine and quinidine.

The new drug:sugar acid salts may be prepared particularly simply by containing a water soluble form of the drug, either the free base or a water soluble salt thereof (e.g. a hydrochloride), with a water soluble form of the sugar acid, optionally in the presence of further counterions which it is desired to precipitate as part of a drug:sugar acid mixed salt. Contacting will generally be effected in a solvent or solvent mixture, optionally a water-miscible solvent system in which drug, sugar acid and salt are all soluble in which case salt precipitation may be effected by addition of water.

Various basic drug compounds do not form water-insoluble sugar acid salts; however it is of course readily determined by simple experimentation whether or not a poorly soluble salt forms.

In general, if a 100mM solution of the drug hydrochloride in ion-exchanged water is mixed with an equinormal amount of sugar acid (i.e. an acid group:drug molecule ratio of 1:1) also in solution in ion-exchanged water, e.g. in a volume about 3/4 of that of the drug solution, a poorly soluble drug:sugar acid salt would precipitate.

The novel salts are particularly advantageously produced by allowing an aqueous solution of the drug base to react with an aqueous solution of sugar acid by titration to obtain the desired stoichiometric ratio.

If it is desired to produce salts in a 1:1 ratio it may be necessary to neutralise excess acid groups in the sugar acid with suitable cations, such as Na^+ , Ca^+ , Mg^{2+} or Al^{3+} . In many instances, the salts thus formed will crystallize spontaneously. If this is not the case the salt may be obtained by evaporation, optionally to

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dryness, or by freeze drying, or by addition of a solvent which is miscible with water, such as methanol or ethanol.

By way of example, a soluble aminoglycoside (e.g. kanamycin A) may be dissolved in water and a solution of SOS may be added thereto. The drug:sugar acid salt separates out as a syrup which can be crystallized from ethanol.

As a further example, to a solution of a tetracyclin (e.g. doxycyclin) in hydrochloric acid there may be added an aqueous solution of SOS-sodium salt. The drug:sugar acid salt precipitates out.

Where inclusion of aluminium as a counterion is desired, the initial aluminium containing aqueous solution should be at a low pH, e.g. about 4, and the precipitation is accomplished by raising the pH, e.g. to 5.5 to 6. The aluminium salt solution may be brought into contact with the drug or drug salt before the sugar acid is added if the drug or drug salt will remain stable in solution in that environment. Otherwise all three components may be brought together simultaneously, optionally with subsequent addition of a base to raise the pH to complete precipitation.

A further option is to effect ion exchange between aluminium, in an insoluble aluminium sugar acid salt, and the drug cations. This requires careful pH control, e.g. to about pH 4, to ensure the exchange reaction occurs.

Thus it is possible to use sucralfate as a starting material. In this case, by way of example the chosen drug is dissolved in water and the pH is adjusted to 4.0. To this solution, an equivalent amount of sucralfate is added with vigorous stirring. An ion exchange reaction takes place whereby the drug forms ion bonds with one or more of the sulphonic acid groups in sucrose-octa-O-sulphonic acid and a corresponding amount of aluminium passes into the aqueous phase. When the

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reaction is completed the novel salts are filtered off and washed with water.

This reaction will only take place in a very narrow pH range, i.e. around pH 4. If pH is higher than 4, the Al-ion is not dissolved and, therefore, it cannot be separated from the reaction product by filtration. If pH is lower than 4, a gel formation takes place which also makes a separation impossible. Furthermore, at too low a pH, the equilibrium may move in such a manner that the drug will remain dissolved.

Thus viewed from a further aspect the invention provides a process for the preparation of poorly water-soluble sugar acid salts of bioactive organic compounds, said process comprising reacting said compound or a salt thereof with said acid or a salt thereof in a solvent system and separating said salt from said system, e.g. by filtration.

The salts can be obtained directly, or via recrystallisation, as surprisingly poorly-soluble, well crystallized material.

Because of the new salts' low solubility in water, the main part of the active drug will be bound to the sugar acid moiety and thus remain biologically inactive during the passage of the oesophagus. This greatly reduces the risk of unfavourable interaction with the mucosa in the oesophagus.

When pharmaceutical formulations are made which contain the new salt for oral use, or peroral administration, the salt can be mixed with a solid pulverised carrier, such as: calcium carbonate, calcium phosphate, calcium crospovidone sulphate, microcrystalline cellulose, cellulose dextrates, dextrin, dextrose excipient, fructose, lactose, mannitol, sorbitol, starch povidone, pregelatinized starch, sucrose, compressible sugar or confectioner's sugar; and can also contain lubricants, such as: calcium stearate, magnesium stearate, polyethylene glycol,

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stearic acid, talc, or zinc stearate. A tabletting mixture may be prepared and mixed with other subsidiary materials before being compressing it into tablets. If coated tablets are desired, then the core - made as outlined above - might be coated with: sodium - carboxymethylcellulose, cellulose acetate, cellulose acetate phthalate, ethylcellulose, gelatin, pharmaceutical glaze, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, methylacrylic acid copolymer, methylcellulose, polyethylene glycol, polyvinyl acetate phthalate, shellac, sucrose, titanium dioxide, carnauba wax, microcrystalline wax or zein which is first dissolved in water an organic solvent or a mixture of solvents. Colouring agents can be added to this dissolution, so that tablets with different strengths can be identified.

Powders and granulates can be made, which contain the new salt alone or mixed with a solid pulverulent carrier, such as: calcium carbonate, calcium phosphate, calcium crospovidone sulphate, microcrystalline cellulose, cellulose, dextran, dextrin, dextrose excipient, fructose, lactose, mannitol, sorbitol, starch, povidone, pregelatinized starch, sucrose, compressible sugar, or confectioner's sugar; and can also contain lubricants, such as: calcium stearate, magnesium stearate, polyethylene glycol, stearic acid, talc, or zinc stearate. The remainder can be comprised of, for example, sweetening agents, such as sugar, aspartame, dextran, dextrose, fructose, mannitol, saccharin, calcium saccharin, sodium saccharin, sorbitol or sucrose.

The powders or granulates may be dissolved and/or dispersed before use. They may also be mixed with a foodstuff before administration.

Soft gelatin capsules can be made, which contain a mixture of the salt and/or vegetable oil. Hard gelatin

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capsules can contain granulates of the salt in combination with a solid pulverulent carrier such as: calcium carbonate, calcium phosphate, calcium crospovidone sulphate, microcrystalline cellulose, cellulose, dextran, dextrin, dextrose excipient, fructose, lactose, mannitol, sorbitol, starch, povidone, pregalatinized starch, sucrose, compressible sugar, or confectioner's sugar, or the new salt alone; and can also contain lubricants, such as: calcium stearate, magnesium stearate, polyethylene glycol, stearic acid, talc, or zinc stearate.

Liquid formulations which may be used for oral use, or peroral administration, may be made in the form of syrups, suspensions, emulsions, or mixtures which can contain up to approximately 20% of the new salt. The remainder can be comprised of, for example, sweetening agents, such as sugar, aspartame, dextran, dextrose, fructose, mannitol, saccharin, calcium saccharin, sodium saccharin, sorbitol or sucrose and a mixture of diluents, like ethanol, water, glycerol and propylene glycol.

The dose in which the new salt is administered is dependant on different factors, like for example the nature of the drug compound and individual needs and administration preferences of each patient. The dosages will generally be on the same level as normally used for the drug compound.

By way of example, dosage units containing 1 to 1000mg, conveniently 50 to 200mg, and preferably about 100mg of the drug compound per unit will be preferred.

For doxycyclin salts, for example, dosages of 100 to 400mg/day of the drug compound will normally be required. As a further example, for the amine glycosides, it will be preferred to administer the novel salts in tablets or capsules which disintegrate in the stomach or duodenum and which each contain from 50 to 250mg, preferably about 100mg, of the amino glycoside

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together with conventional adjuvants and/or carriers.

The dissolution properties of the new salts according to the invention can easily be demonstrated by the method described in the Examples below.

By modifying the composition of the new salts according to the invention, it is possible to change the dissolution properties in order to optimize the compositions with regard to the dissolution profile desired.

The new salts according to the present invention can also be used locally on the skin, or mucous membranes formulated as creams, lotions, ointments, or gels. As an example, doxycyclin sucrose octasulphate is well suited for insertion in or around the periodontal pocket of an individual suffering from periodontitis. In this case, the vehicle described in US-A-5143934 (Dumex) is especially advantageous to use as a carrier.

In the accompanying drawings, Figure 1 is a plot of dissolution rate for doxycyclin.SOS salt according to the invention compared with the commercial product Vibramycin, Figure 2 is a schematic representation of apparatus used for the determination of drug retention on gastrointestinal mucous membrane, and Figure 3 is a schematic representation of apparatus which may be used to evaluate bioadhesion by tensiometry.

The bioadhesion properties of the drug:sugar acid salts of the invention may be tested in vitro on the test systems described below with reference to Figures 2 and 3 of the accompanying drawings.

1. In vitro test system for bioadhesion by means of rabbit jejunum membranes

The bioadhesive test system described in the following is a modified system of a method described by Ranga Rao and Buri, 1989.

Male albino rabbits (3-4 kg) (New Zealand white rabbit SSC:CPH) were fasted for 20 hours before they

were killed by means of a pentobarbital sodium injection. The intestines of the rabbits were dissected, and placed in an isotonic 0.9% sodium chloride solution at ambient temperature (about 18°C). Within 30 minutes the jejunums were cut and washed with 0.9% sodium chloride solution. The lumens were gently rinsed with the saline until the intestines were clean. The jejunums were cut into pieces of 8-9 cm and immediately frozen (-20°C). The intestines were stored up to 3 months before use. Before testing, the segment of jejunum was gently thawed out.

The segment of jejunum was cut longitudinally. It was placed on a stainless steel support (a tube of 2 cm in diameter and cut longitudinally at its centre) with the mucosa layer facing up, spread and held in position on the support by the adhesive effect of the jejunum itself. The support with the jejunum was placed at an angle of -7 to -21° in a cylindrical cell thermostated at 37°C. A schematic description of the cell is shown in Fig. 2. The relative humidity in the thermostatic cell was kept at 100%. The intestines were then flushed with isotonic 0.02 M phosphate buffer solution (pH 6.5, 37°C) for 5 minutes at a flow rate of 10 ml min⁻¹, using a peristaltic pump, to equilibrate the intestine with the buffer and to rinse off loose mucosa. An accurately weighed amount of the sample to be tested for bioadhesiveness (about 50-150 mg) was placed evenly on the mucosa of the jejunum (0.8 x 6 cm). About 1 ml of the buffer solution was carefully dropped evenly onto the sample to ensure hydration. Immediately after, the segments were left for 10 minutes in the cell allowing the sample to interact with the glycoproteins of the jejunum and to prevent drying of the mucus. After 10 minutes the segments were evenly flushed with the isotonic 0.02 M phosphate buffer solution (pH 6.5, 37°C) for 30 minutes at a constant flow rate of 5-15 ml min⁻¹. The tip of the tube carrying the buffer solution was

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placed 3-4 mm above the jejunum to ensure an even liquid flow over the mucosa. The effluent was collected into a beaker. The amount of bioadhesive component remaining on the jejunum was calculated either by measuring the amount of compound remaining on the jejunum or by measuring the amount in the receiver by means of HPLC. Other tissue than rabbit jejunum may be applied. E.g. buccal mucosa, stomach, intestine obtained from e.g.. pig, rat and rabbit.

2. In vitro test system for bioadhesion by means of tensiometry

The test system for bioadhesion described in the following is a modified system of a method described by Tobyn, Johnson and Gibson (in "Use of a TA.XT2 Texture Analyser in Mucoadhesive Research", International LABMATE, 1992, XVII (issue VI), 35-38).

The test system involves measuring the tensile force required to break an adhesive bond formed between a model membrane and a test sample (i.e the sample which is tested for its bioadhesive properties).

The test apparatus employed in the following is a TA.XT2 Texture analyser (Stable Micro System Ltd., Haslemere, UK) (Figure 3). The test enables measuring the strength of adhesive bonding established by contacting a model membrane, i.e. in this case a rabbit intestine segment, and the test sample. An analogous test apparatus may also be employed.

The TA.XT2 Texture analyser apparatus is equipped with an instrument probe 7 (see Figure 3) on a sliding stand 14 which is movable in a vertical direction at a variable rate under the control of a motor and displacement transducer 15 operated by control unit 17 and computer 17. During the so-called withdrawal phase of the testing, the instrument probe is moved upwards with a constant rate until detachment occurs (see below). Furthermore, the apparatus is equipped with a

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stationary place 8 on which a first holder 9 is placed. Before and during a test run, a model membrane 10 is fixed on this holder, e.g. by means of a cap or double adhesive tape or glue. The holder is constructed so that a well-defined area of the model membrane (about 0.5-9 cm²) is used in the test runs. The accurate size of the exposed area is used in the calculation of the adhesive strength (see below).

As mentioned above, the test involves employment of a model membrane, primarily of animal origin. The membrane could be e.g. rabbit, rat or pig gastric mucosa; a segment of rabbit, rat or pig intestines, e.g. a segment of rabbit jejunum; or a segment of rabbit, rat or pig intestines from which the mucosal layer has been removed prior to testing; or skin from an animal (after removal of substantially all subcutaneous fat); or it could be artificial or commercial available mucin.

In the test described below, a model membrane of a segment of rabbit intestines, i.e. a segment of rabbit jejunum has been employed. However, it is appreciated that a change of membrane in some case may be advantageous, e.g. if a relatively large surface area of a model membrane is required. If the results obtained by use of another membrane than the rabbit intestine model membrane are used to compare the bioadhesive properties of various substances or combinations, the results of a reference compound could be included. As discussed below testing of a reference sample may also be made as a routine. Polycarbophil and Carbopol 934 have been found suitable as reference compounds.

A test sample (about 50-500 mg) is applied in a uniform layer either

- i) on the luminal side of the model membrane 10 placed on the first holder 9, or

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ii) directly on the instrument probe 7, if necessary by means of a double adhesive tape or glue applied on the instrument probe before application of the test sample.

In those cases where it is not possible to fix the test sample to the instrument probe, the apparatus may be equipped with a second holder 11 on which another model membrane is fixed. In such cases, the model membranes employed on the two holders are usually of the same type (e.g. segments of rabbit jejunum). It is also possible to fix the other model membrane directly to the instrument probe e.g. by means of a double adhesive tape or glue.

Test runs are usually performed in an aqueous medium and the temperature is maintained at 37°C by use of a thermostatically controlled heater/stirrer 12. The aqueous medium is contained in a vessel 13. Prior to testing, the model membrane and the test sample is allowed to equilibrate with the aqueous medium for about 5-30 minutes. The aqueous medium is usually added during or after the initial test phase in which the two substrates (i.e. the model membrane and the test sample) are gently contacted with each other by means of lowering the instrument probe. As aqueous medium is used isotonic 0.02 M phosphate buffer solution, pH 6.5 but it may be replaced by other aqueous solutions.

In some cases it is desirable to avoid testing in an aqueous medium (e.g. in those cases where the test sample has a relatively low dynamic viscosity); however, in order to avoid drying of the model membrane, a solvent evaporation trap may be employed, whereby the temperature (about 37°C) and the humidity (at least about 80%) are controlled during testing. In those cases where the test sample can form a fluid crystalline phase, it may also be necessary to add a sufficient amount of water in order to induce formation of such a fluid crystalline phase.

Test runs are performed as follows:

The instrument probe (either with or without a second holder 11) is lowered in order to bring the model membrane and the test sample in contact under a constant force (preload of 0.05-2 N). After a time period of about 30 sec-3 minutes of contact time, the withdrawal phase is initiated by applying a vertically acting force by raising the instrument probe at a constant speed of about $0.1-0.2 \text{ mm sec}^{-1}$ until the two substrates (i.e. the model membrane as a first substrate and the test sample as a second substrate) are completely detached. The force required for detachment is recorded. Data is continuously collected and calculations are performed by means of a software program "XTRA-Dimension software package" available from Stable Micro Systems, UK. The maximum force of detachment represents the adhesion strength (N cm^{-2}) and the area under the force/time (or force/distance) curve is considered as the adhesion work (mJ).

Determination of the bioadhesive properties of a test sample

In order to test whether a test sample is bioadhesive, two test runs are performed:

1. A test run without any test sample applied (result: adhesion strength T_0)
2. A test run with the test sample applied (result: adhesion strength T).

In both cases the adhesion strength is calculated and the test sample is considered bioadhesive if $T/T_0 \times 100\%$ is at least 115%, such as 125%, 135%, 150%, 175%, 200%.

Alternatively, a test run with the test sample is performed and the results are compared with the results

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of testing known bioadhesive substances such as, e.g. polycarbophil (a strong bioadhesive substance), or chitosan, tragacanth, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), karaya gum, carboxymethylcellulose (CMC), gelatin, pectin, acacia, PEG 6000, povidone, or DEAE-dextran (less bioadhesive than polycarbophil).

Polycarbophil (Noveon™ AA-1, BF Goodrich, Hounslow, U.K.) is a high molecular weight poly(acrylic acid) copolymer loosely cross-linked with divinyl glycol. On account of its known excellent mucoadhesive properties, this polymer serves as a reference. Before testing in the above-mentioned tensiometric test, a polycarbophil gel is prepared by mixing polycarbophil with water (resulting concentration about 10-20 mg ml⁻¹) and the mixture is allowed to hydrate at 37°C for 24 hours. The polymer solution is periodically stirred. The pH is adjusted to 5.1 using either diluted sodium hydroxide or hydrochloric acid. The resulting gel is tested as described above and the result obtained is used as a reference value for excellent bioadhesive substances. Similarly, other substances which are known bioadhesive substances are tested, and by choosing test substances with various degrees of bioadhesiveness so that an evaluation scale can be made, the performance of a test sample with respect to bioadhesiveness can be evaluated. It is contemplated that the following scale is applicable (force resolution 0.1 gm):

Bioadhesive properties	Adhesion force (mN cm ⁻²)
none	less than 0.1 mN cm ⁻²
poor	about 0.1 - about 1 mN cm ⁻²
moderate	about 1 - about 4 mN cm ⁻²
good	about 4 - about 10 mN cm ⁻²
excellent	more than 10 mN cm ⁻²

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In some cases, e.g. in the case of tablets with excellent bioadhesive properties, an adhesion force may be as high as 25 about 700 mN cm^{-2} or even higher.

3. In vitro test system for bioadhesion by means of tensiometry - determination of duration of adhesion

The test system described in the following is a modified system of a method described by Smart (Int. J Pharm. 73:69-74 (1991)).

The apparatus and conditions employed in this test are the same as described in the test denoted 2 above.

The duration of adhesion is evaluated by applying a constant tensile force between about $0.25-2 \text{ N cm}^{-2}$, such as 1 N cm^{-2} , to the adhesion bond after the initial contact time (see above: 0.5-3 minutes) and leaving for up to 8 hours or until the bond fractures. Every hour the tensile force acting on the adhesive joint is noted and if necessary adjusted to the initial value (eg 1 N cm^{-2}). After 8 hours the force required to break the adhesive bond is evaluated.

All publications referred to hereinbefore are incorporated herein by reference.

The invention will now be described by reference to the following non-limiting Examples.

EXAMPLE 1

Sucrose-octa-O-sulphonic acid

60g (50mmol) of sucrose-octa-O-sulphonic acid sodium salt (produced in accordance with J. Chem. Soc. Faraday Trans., 1981, 77, pages 629-639) are dissolved in 200ml of water and cation exchanged on Amberlite[®] IR (H^+). The combined eluates are diluted to 1 litre corresponding to an 0.05 M solution.

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EXAMPLE 2

Doxycyclin sucrose-octa-O-sulphonic acid salt

18.5g (40mmol) doxycyclin monohydrate is dissolved in 400ml 0.1 M HCl and by addition of 6.5g (5mmol), sucrose-octa-O-sulphonic acid-Na₈, 8 aq., dissolved in 300ml water, precipitation of doxycyclin sucrose octasulphate takes place. The reaction mixture is stirred for 60min at 25°C, filtered, washed with 3x50ml water by dispersion and refiltration and vacuum dried at 1 Torr/25°C/sicapent°/20h.

Yield: 23.5g.

MP.: 150°C (decomp.).

Stoichiometric proportions: in the batches produced, the content of water was found to be about 10%. The content of doxycyclin was found to be about 77%, calculated with reference to the dried substance. This content of doxycyclin indicates that 8 moles of doxycyclin complex with 1 mole of sucrose-octa-O-sulphonic acid.

EXAMPLE 3

Doxycyclin SOS salt

20.5g doxycyclin hydclate (40mmol) is dissolved in 400ml water and with vigorous stirring, 100ml of the acid solution of Example 1 is added. After 30min, the pH is adjusted to 3.5 with 0.1 M NaOH solution. After another 30min of stirring, the precipitate is filtered and dried as in Example 2.

EXAMPLE 4

Doxycyclin SOS salt

18.5g (40mmol) doxycyclin monohydrate is dissolved

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in 400ml 0.1 M HCl and by titration with 100ml 0.05 M (5mmol) sucrose-octa-O-sulphonic acid, precipitation of doxycyclin sucrose octa sulphate takes place. The reaction mixture is stirred for 60min at 25°C, filtered, washed with 3x50ml water (by dispersion and refiltration) and vacuum dried at 1 Torr/25°C/sicapent®/20h.

EXAMPLE 5

Doxycyclin SOS salt

By titration of 6.5g (5mmol) sucrose-octa-O-sulphonic acid Na₈, 8aq. dissolved in 300ml water, with 18.5g (40mmol) doxycyclin monohydrate dissolved in 400ml 0.1 M HCl, precipitation of doxycyclin sucrose octasulphate takes place. The reaction mixture is stirred for 60min at 25°C, filtered, washed with 3x50ml water (by dispersion and refiltration) and vacuum dried at 1 Torr/25°C/sicapent®/20h.

EXAMPLE 6

Dissolution of doxycyclin sucrose octasulphate

The paddle method is used in accordance with USP XXII, p. 1579, (apparatus II), with 900ml 0.1 N HCl. One tablet containing 150mg doxycyclin sucrose octasulphate (equal to 105mg doxycyclin) is placed in the dissolution apparatus. Samples are taken after 5, 10, 20, 30 and 60 minutes and diluted.

The samples are analyzed spectrophotometrically at 345.9nm in a Shimadzu 160 A photometer.

The results are compared to samples of Vibramycin® from Pfizer, which contains doxycyclin carragenate.

In Figure 1, the plot of release versus time is illustrated graphically. This shows that the delayed release characteristics are similar despite the major differences in the counterion.

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In Figure 1, data points for Vibramycin are indicated by solid squares (■), for Doxycyclin without Tween by hollow squares (□) and for Doxycyclin with Tween by solid diamonds (◆). The data point values are set out in Table 2 below:

TABLE 2

Comparison of Vibramycin and Doxycyclin-SOS
Tablets 100 MG

Time	Vibramycin	Doxyc. with tween	Doxyc. without Tween
0	0	0	
5	37.45	45.89	42.02
10	56.06	56.12	57.22
20	76.75	73.31	79.54
30	88.08	81.42	91.06
60	98.67	94.76	104.29

EXAMPLE 7

The reaction of a drug:sugar acid salt of the invention with water is a swelling reaction whereby a sticky substance or syrup is formed. The absorption of water occurs to a certain point where the particles have become an oily, viscous fluid which has comparatively low solubility in water. When a drop of this fluid is applied to smooth skin, a membrane is formed which has low solubility in water and which may only be removed by intensive scrubbing with water. By rinsing with ion-containing water, the membrane is gradually dissolved until it disappears completely.

EXAMPLE 8

Test for bioadhesion on mucosal surfaces

The bioadhesion of the novel salts according to the

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invention is demonstrated in the test system shown in Figure 2 wherein (1) is thermostatic water flow at 40°C, (2) is a reservoir containing the washing solution at 37°C, (3) is a peristaltic pump, (4) is a stainless steel support, (5) is a model membrane, and (6) is a receiver for collecting the washings.

A segment of jejunum from rabbit is placed on a support (4) with the mucosa facing upwards, spread and held in position on the support by the adhesive effect of the jejunum itself. Support and jejunum are placed at an angle of -7°C in a cylindrical cell thermostated at 37°C. The sample to be tested is placed on the jejunum and 1ml buffer is dropped thereon. The buffer used is either a 0.01 M HCl solution, pH 2 (buffer a) or borate buffer solution 0.05 M, pH 7.4 (buffer b). The segments are left for 10 minutes in the cell to allow the test substance to interact with the glycoproteins of the mucosa. After 10 minutes the jejunum is flushed with either buffer a or b for 30 minutes.

The buffer is collected in a receiver (6). The amount of test substance remaining on the jejunum is calculated by measuring the amount in the receiver by means of HPLC.

EXAMPLE 9

Diltiazem Salt of Sucrose-octa-O-sulphonic Acid

16.7109 g (37.0546 mmol) Diltiazem-HCl is dissolved in 400 ml ion-exchanged water (pH 4.42) and by addition of 6.5281 g (5.6344 mmol) sucrose-octa-O-sulphonic acid-Na₈, 8 aq., dissolved in 200 ml ion-exchanged water, precipitation takes place. The reaction mixture is filtered and vacuum dried at 1Torr/25°C/20h/Sicapent®.

Yield: 19.1166 g

DSC showed decomposition from 170°C.

Water content: 3.9%

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EXAMPLE 10

Cyclobenzaprine Salt of Sucrose-octa-O-sulphonic Acid

Analogously to Example 9, using 12.4763 g (40.0087 mmol) Cyclobenzaprine.HCl in 400 ml ion-exchanged water (pH 4.15) and 5.8159 g (5.0198 mmol) sucrose-octa-O-sulphonic acid-Na₈, 8 aq., in 300 ml ion-exchanged water.

Yield: 4.5709 g

DSC showed decomposition from 200°C.

EXAMPLE 11

Noscapine Salt of Sucrose-octa-O-sulphonic Acid

Analogously to Example 9, using 17.9965 g (40.0020 mmol) Noscapine.HCl in 400 ml ion-exchanged water (pH 3.86) and 5.7910 g (4.9983 mmol) sucrose-octa-O-sulphonic acid-Na₈, 8 aq., in 300 ml ion-exchanged water.

Yield: 17.0296 g

DSC showed decomposition from 200°C.

EXAMPLE 12

Amitriptyline salt of Sucrose-octa-O-Sulphonic Acid

Analogously to Example 9, using 12.5245 g (39.9009 mmol) Amitriptyline.HCl in 400 ml ion-exchanged water (pH 3.73) and 5.7715 g (4.9814 mmol) sucrose-octa-O-sulphonic acid-Na₈, 8 aq., in 300 ml ion-exchanged water.

Yield: 2.1166 g

EXAMPLE 13

Chlordiazepoxide salt of Sucrose-octa-O-Sulphonic Acid

Analogously to Example 9, using 13.4300 g (39.9370 mmol) Chlordiazepoxide.HCl in 400 ml ion-exchanged water

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(pH 3.08) and 5.7774 g (4.9865 mmol) sucrose-octa-O-sulphonic acid-Na₈, 8 aq., in 300 ml ion-exchanged water.

Yield: 21.8657 g

EXAMPLE 14

Erythromycin Salt of Sucrose-octa-O-sulphonic Acid

9.9861 g (6.8941 mmol) Erythromycin Lactobionate is dissolved in 400 ml ion-exchanged water (pH 6.74). The solution is adjusted to pH 4.00 with 1M HCl (pH 4.33). A solution of 1.0021 g (0.8649 mmol) sucrose-octa-O-sulphonic acid-Na₈, 8 aq., in 300 ml ion-exchanged water is added, which results in precipitation. The reaction mixture is filtered and vacuum dried at 1Torr/25°C/20h/Sicapent®.

Yield: 3.8896 g

DSC showed decomposition from 200°C.

EXAMPLE 15

Imipramine Salt of Sucrose-octa-O-sulphonic Acid

Analogously to Example 14, using 3.9789 g (12.5573 mmol) Imipramine-HCl in 200 ml ion-exchanged water (pH 5.46) and 1.8809 g (1.6234 mmol) sucrose-octa-O-sulphonic acid-Na₈, 8 aq., in 100 ml ion-exchanged water.

Yield: 0.7618 g

EXAMPLE 16

Nortriptyline Salt of Sucrose-octa-O-sulphonic Acid

Analogously to Example 14, using 0.7358 g (2.4540 mmol) Nortriptyline-HCl in 100 ml ion-exchanged water (pH 6.22) and 0.3647 g (0.3148 mmol) sucrose-octa-O-sulphonic acid-Na₈, 8 aq., in 100 ml ion-exchanged water.

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Yield: 0.7844 g

DSC showed decomposition from 190°C.

EXAMPLE 17

Quinidine Salt of Sucrose-octa-O-sulphonic Acid

Analogously to Example 14, using 3.8360 g (5.1357 mmol) Quinidine Sulphate in 400 ml ion-exchanged water (pH 6.29) and 0.7505 g (0.6478 mmol) sucrose-octa-O-sulphonic acid-Na₈, 8 aq., in 100 ml ion-exchanged water.

Yield: 1.4638 g

DSC showed decomposition from 175°C.

EXAMPLE 18

Benztropine Salt of Sucrose-octa-O-sulphonic Acid

Analogously to Example 14, using 4.0353 g (9.5739 mmol) Benztropine Mesylate in 300 ml ion-exchanged water (pH 6.23) and 1.4011 g (1.2093 mmol) sucrose-octa-O-sulphonic acid-Na₈, 8 aq., in 150 ml ion-exchanged water.

Yield: 3.0020 g

EXAMPLE 19

Verapamil Salt of Sucrose-octa-O-Sulphonic Acid

Analogously to Example 14, using 0.7512 g (1.5298 mmol) Verapamil·HCl in 200 ml ion-exchanged water (pH 6.17) and 0.2226 g (0.1921 mmol) sucrose-octa-O-sulphonic acid-Na₈, 8 aq., in 100 ml ion-exchanged water.

Yield: 0.2791 g

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EXAMPLE 20

Chlorpromazine salt of Sucrose-octa-O-Sulphonic Acid

Analogously to Example 14, using 11.8682 g (33.3949 mmol) Chlorpromazine-HCl in 400 ml ion-exchanged water (pH 5.10) and 4.9071 g (4.2354 mmol) sucrose-octa-O-sulphonic acid-Na₈, 8 aq., in 300 ml ion-exchanged water.

Yield: 8.2810 g

EXAMPLE 21

Diphenhydramine salt of Sucrose-octa-O-Sulphonic Acid

Analogously to Example 14, using 5.9032 g (20.2268 mmol) Diphenhydramine-HCl in 200 ml ion-exchanged water (pH 5.42) and 2,9330 g (2,5315 mmol) sucrose-octa-O-sulphonic acid-Na₈, 8 aq., in 150 ml ion-exchanged water.

EXAMPLE 22

Tobramycin salt of Sucrose-octa-O-Sulphonic Acid

Analogously to Example 14, using 18.6368 g (39.8614 mmol) Tobramycin in 400 ml ion-exchanged water (pH 10.36) and 5,7753 g (4,9847 mmol) sucrose-octa-O-sulphonic acid-Na₈, 8 aq., in 300 ml ion-exchanged water.

Yield: 9.5791 g

EXAMPLE 23

Bacitracin Salt of Sucrose-octa-O-sulphonic Acid

11.8176 g (8.3074 mmol) Bacitracin is dissolved in 400 ml 0.1M HCl (pH 2.16) and by addition of 5.7098 g (4.9282 mmol) sucrose-octa-O-sulphonic acid-Na₈, 8 aq., dissolved in 300 ml ion-exchanged water, precipitation takes place. The reaction mixture is filtered and vacuum

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dried at 1Torr/25°C/20h/Sicapent®.

Yield: 7.5705 g

DSC showed decomposition from 150°C.

EXAMPLE 24

Polymyxin Salt of Sucrose-octa-O-sulphonic Acid

Analogously to Example 23, using 10.0453 g (8.3711 mmol) Polymyxin in 400 ml 0.1M HCl (pH 1.60) and 1.2384 g (1.0689 mmol) sucrose-octa-O-sulphonic acid-Na₈, 8 aq., in 200 ml ion-exchanged water.

Yield: 4.3644 g

DSC showed decomposition from 160°C.

EXAMPLE 25

Vancomycin Salt of Sucrose-octa-O-sulphonic Acid

Analogously to Example 23, using 7.6646 g (5.2888 mmol) Vancomycin in 200 ml 0.1M HCl (pH 1.58) and 0.8011 g (0.6914 mmol) sucrose-octa-O-sulphonic acid-Na₈, 8 aq., in 100 ml ion-exchanged water.

Yield: 2.8677 g

DSC showed decomposition from 135°C.

EXAMPLE 26

Flunarizine Salt of Sucrose-octa-O-sulphonic Acid

Analogously to Example 23, using 0.7635 g (1.5992 mmol) Flunarizine·2HCl in 200 ml 0.1M HCl (pH 1.31) and 0.2414 g (0.2084 mmol) sucrose-octa-O-sulphonic acid-Na₈, 8 aq., in 100 ml ion-exchanged water.

Yield: 0.6669 g

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EXAMPLE 27

Doxycyclin salt of Sucrose-octa-O-Sulphonic Acid

Analogously to Example 23, using 18.4004 g (39.7838 mmol) Doxycyclin monohydrate in 400 ml 0.1M HCl (pH 1.16) and 6.5185 g (5.6262 mmol) sucrose-octa-O-sulphonic acid-Na₈, 8 aq., in 300 ml ion-exchanged water.

Yield: 21,1633 g

EXAMPLE 28

Cinnarizine salt of Sucrose-octa-O-Sulphonic Acid

Analogously to Example 23, using 7.3713 g (20.0035 mmol) Cinnarizine in 400 ml 1M HCl (pH 0.05) and 2.9450 g (2.5419 mmol) sucrose-octa-O-sulphonic acid-Na₈, 8 aq., in 250 ml ion-exchanged water.

Yield: 1,0216 g

EXAMPLE 29

Ergotamine Salt of Sucrose-octa-O-sulphonic Acid

1.0189 g (0.7758 mmol) Ergotamine Tartrate is dissolved in 400 ml 0.1M HCl (pH 1.62). The compound is almost insoluble, so the solution has to be decanted. A solution of 0.1302 g (0.1124 mmol) sucrose-octa-O-sulphonic acid-Na₈, 8 aq., in 100 ml ion-exchanged water is added, which results in precipitation. The reaction mixture is filtered and vacuum dried at 1Torr/25°C/20h/ Sicapent®.

Yield: 0.5549 g

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EXAMPLE 30

Furosemide salt of Sucrose-octa-O-Sulphonic Acid

13.2759 g (40.1363 mmol) Furosemide is dissolved in 400 ml methanol (pH 3.82) and by addition of 5.8505 g (5.0496 mmol) sucrose-octa-O-sulphonic acid-Na₈, 8 aq., dissolved in 300 ml ion-exchanged water, precipitation takes place. The reaction mixture is filtered and vacuum dried at 1Torr/25°C/20h/Sicapent°.

Yield: 9.9696 g

EXAMPLE 31

Cyproheptadiene salt of Sucrose-octa-O-Sulphonic Acid

Analogously to Example 30, using 0.4260 g (1.2141 mmol) Cyproheptadiene-HCl sesquihydrate in 100 ml methanol (pH 4.80) and 0.1850 g (0.1597 mmol) sucrose-octa-O-sulphonic acid-Na₈, 8 aq., in 100 ml ion-exchanged water.

EXAMPLE 32

Carbamazepine salt of Sucrose-octa-O-Sulphonic Acid

9.4229 g (39.8836 mmol) Carbamazepine is dissolved in 400 ml methanol (pH 7.70). The solution is adjusted to pH 4.00 with 1M HCl (pH 2.03). A solution of 5.7700 g (4.9801 mmol) sucrose-octa-O-sulphonic acid-Na₈, 8 aq., in 300 ml ion-exchanged water is added, which results in precipitation. The reaction mixture is filtered and vacuum dried at 1Torr/25°C/20h/Sicapent°.

EXAMPLE 33

Indomethacin salt of Sucrose-octa-O-Sulphonic Acid

Analogously to Example 32, using 14.3550 g (40.1191 mmol) Indomethacin in 400 ml absolute ethanol (pH 5.02)

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and 5.8419 g (5.0422 mmol) sucrose-octa-O-sulphonic acid-Na₈, 8 aq., in 300 ml ion-exchanged water.

Yield: 1.3736 g

EXAMPLE 34

Amitriptyline salt of Dextran Sulphate 5000

1.0145 g (3.2320 mmol) Amitriptyline-HCl is dissolved in 100 ml ion-exchanged water (pH 4.20) and by addition of 100 ml 0.004M Dextran sulphate-solution (MW = 5000 g/mol), precipitation takes place. The reaction mixture is filtered and vacuum dried at 1Torr/25°C/20h/ Sicapent®.

Yield: 0.5376 g

EXAMPLE 35

Chlordiazepoxide salt of Dextran Sulphate 5000

Analogously to Example 34, using 1.0639 g (3.1637 mmol) Chlordiazepoxide-HCl in 100 ml ion-exchanged water (pH 3.24) and 100 ml 0.004M dextran sulphate-solution.

Yield: 0.2663 g

EXAMPLE 36

Cyclobenzaprine salt of Dextran Sulphate 5000

Analogously to Example 34, using 1.0049 g (3.2225 mmol) Cyclobenzaprine-HCl in 100 ml ion-exchanged water (pH 4.60) and 100 ml 0.004M dextran sulphate-solution.

Yield: 0.8785 g

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EXAMPLE 37

Diltiazem salt of Dextran Sulphate 5000

Analogously to Example 34, using 1.5210 g (3.3727 mmol) Diltiazem·HCl in 100 ml ion-exchanged water (pH 4.82) and 100 ml 0.004M dextran sulphate-solution.

Yield: 1.4716 g

EXAMPLE 38

Noscapine salt of Dextran Sulphate 5000

Analogously to Example 34, using 1.4347 g (3.1894 mmol) Noscapine·HCl in 100 ml ion-exchanged water (pH 3.94) and 100 ml 0.004M dextran sulphate-solution.

Yield: 1.1743 g

EXAMPLE 39

Vancomycin salt of Dextran Sulphate 5000

Analogously to Example 34, using 4.7484 g (3.1959 mmol) Vancomycin·HCl in 100 ml ion-exchanged water (pH 3.59) and 100 ml 0.004M dextran sulphate-solution.

Yield: 3.3145 g

EXAMPLE 40

Benztropine salt of Dextran Sulphate 5000

0.4958 g (1.1763 mmol) Benztropine Mesylate is dissolved in 50 ml ion-exchanged water (pH 6.68). The solution is adjusted to pH 4.00 with 1M HCl (pH 3.37). A solution of 100 ml 0.004M dextran sulphate is added, which results in precipitation. The reaction mixture is filtered and vacuum dried at 1Torr/25°C/20h/Sicapent®.

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Yield: 0.3437 g

EXAMPLE 41

Chlorpromazine salt of Dextran Sulphate 5000

Analogously to Example 40, using 1.1420 g (3.2134 mmol) Chlorpromazine·HCl in 100 ml ion-exchanged water (pH 5.16) and 100 ml 0.004M dextransulphate-solution.

Yield: 1.0111 g

EXAMPLE 42

Diphenhydramine salt of Dextran Sulphate 5000.

Analogously to Example 40, using 0.9352 g (3.2044 mmol) Diphenhydramine·HCl in 100 ml ion-exchanged water (pH 5.94) and 100 ml 0.004M dextransulphate-solution.

EXAMPLE 43

Imipramine salt of Dextran Sulphate 5000

Analogously to Example 40, using 0.3532 g (1.1147 mmol) Imipramine·HCl in 50 ml ion-exchanged water (pH 6.89) and 100 ml 0.004M dextransulphate-solution.

Yield: 0.3910 g

EXAMPLE 44

Propranolol salt of Dextran Sulphate 5000

Analogously to Example 40, using 0.3874 g (1.3097 mmol) Propranolol·HCl in 100 ml ion-exchanged water (pH 6.51) and 100 ml 0.004M dextransulphate-solution.

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EXAMPLE 45

Quinidine salt of Dextran Sulphate 5000

Analogously to Example 40, using 2.4408 g (3.2678 mmol) Quinidine Sulphate in 400 ml ion-exchanged water (pH 6.49) and 100 ml 0.004M dextransulphate-solution.

Yield: 1.3666 g

EXAMPLE 46

Tobramycin salt of Dextran Sulphate 5000

Analogously to Example 40, using 1.5094 g (3.2284 mmol) Tobramycin in 100 ml ion-exchanged water (pH 10.51) and 100 ml 0.004M dextransulphate-solution.

EXAMPLE 47

Verapamil salt of Dextran Sulphate 5000

Analogously to Example 40, using 1.5760 g (3.2095 mmol) Verapamil·HCl in 100 ml ion-exchanged water (pH 6.59) and 100 ml 0.004M dextransulphate-solution.

Yield: 0.8699 g

EXAMPLE 48

Bacitracin salt of Dextran Sulphate 5000

4.5222 g (3.1790 mmol) Bacitracin is dissolved in 200 ml 1M HCl (pH 0.27) and by addition of 100 ml 0.004M dextransulphate-solution, precipitation takes place. The reaction mixture is filtered and vacuum dried at 1Torr/25°C/20h/Sicapent®.

Yield: 2.7685 g

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EXAMPLE 49

Cinnarizine salt of Dextran Sulphate 5000

Analogously to Example 48, using 1.1928 g (3.2369 mmol) Cinnarizine in 100 ml 1M HCl (pH 0.29) and 100 ml 0.004M dextran sulphate-solution.

Yield: 0.4301 g

EXAMPLE 50

Doxycyclin salt of Dextran Sulphate 5000

Analogously to Example 48, using 1.4734 g (3.1860 mmol) Doxycyclin monohydrate in 100 ml 1M HCl (pH 0.07) and 100 ml 0.004M dextran sulphate-solution.

Yield: 0.7362 g

EXAMPLE 51

Ergotamine salt of Dextran Sulphate 5000

Analogously to Example 48, using 0.6530 g (0.4972 mmol) Ergotamine Tartrate in 500 ml 1M HCl (pH 0.51) and 100 ml 0.004M dextran sulphate-solution.

Yield: 0.3641 g

EXAMPLE 52

Pindolol salt of Dextran Sulphate 5000

Analogously to Example 48, using 0.8004 g (3.2233 mmol) Pindolol in 100 ml 1M HCl (pH 0.26) and 100 ml 0.004M dextran sulphate-solution.

Yield: 0.2074 g

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EXAMPLE 53

Polymyxin salt of Dextran Sulphate 5000

Analogously to Example 48, using 3.7728 g (3.1440 mmol) Polymyxin in 100 ml 1M HCl (pH 0.12) and 100 ml 0.004M dextransulphate-solution.

Yield: 4.4188 g

EXAMPLE 54

Furosemide salt of Dextran Sulphate 5000

1.0512 g (3.1780 mmol) Furosemid is dissolved in 100 ml methanol (pH 3.67) and by addition of 100 ml 0.004M dextranesulphate-solution, precipitation takes place. The reaction mixture is filtered and vacuum dried at 1Torr/25°C/20h/Sicapent®.

Yield: 0.5109 g

EXAMPLE 55

Diclofenac salt of Dextran Sulphate 5000

1.0491 g (3.2977 mmol) Diclofenac-Na is dissolved in 100 ml ethanol (pH 9.49). The solution is adjusted to pH 4.00 with 1M HCl (pH 2.28). A solution of 100 ml 0.004M dextransulphate is added, which results in precipitation. The reaction mixture is filtered and vacuum dried at 1Torr/25°C/20h/Sicapent®.

Yield: 0.5857 g

EXAMPLE 56

Amitriptyline salt of Dextran Sulphate 12000

0.3305 g (1.0529 mmol) Amitriptyline-HCl is dissolved in 100 ml ion-exchanged water (pH 4.55) and by

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addition of 100 ml 0.00125M Dextransulphate-solution (MW = 12000 g/mol), precipitation takes place. The reaction mixture is filtered and vacuum dried at 1Torr/25°C/20h/Sicapent®.

Yield: 0.2269 g

EXAMPLE 57

Noscapine salt of Dextran Sulphate 12000

Analogously to Example 56, using 0.4908 g (1.0909 mmol) Noscapine·HCl in 100 ml ion-exchanged water (pH 4.39) and 100 ml 0.00125M dextransulphate-solution.

Yield: 0.2546 g

EXAMPLE 58

Benztropine salt of Dextran Sulphate 12000

0.4338 g (1.0292 mmol) Benztropine Mesylate is dissolved in 100 ml ion-exchanged water (pH 6.51). The solution is adjusted to pH 4.00 with 1M HCl (pH 3.60) and by addition of 100 ml 0.00125M dextransulphate-solution, precipitation takes place. The reaction mixture is filtered and vacuum dried at 1Torr/25°C/20h/Sicapent®.

Yield: 0.3063 g

EXAMPLE 59

Chlorpromazine salt of Dextran Sulphate 12000

Analogously to Example 58, using 0.3621 g (1.0189 mmol) Chlorpromazine·HCl in 100 ml ion-exchanged water (pH 5.89) and 100 ml 0.00125M dextransulphate-solution.

Yield: 0.3828 g

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EXAMPLE 60

Cyclobenzaprine salt of Dextran Sulphate 12000

Analogously to Example 58, using 0.3202 g (1.0268 mmol) Cyclobenzaprine·HCl in 100 ml ion-exchanged water (pH 5.50) and 100 ml 0.00125M dextransulphate-solution.

Yield: 0.2957 g

EXAMPLE 61

Diltiazem salt of Dextran Sulphate 12000

Analogously to Example 58, using 0.4612 g (1.0227 mmol) Diltiazem·HCl in 100 ml ion-exchanged water (pH 5.44) and 100 ml 0.00125M dextransulphate-solution.

Yield: 0.2907 g

EXAMPLE 62

Diphenhydramine salt of Dextran Sulphate 12000

Analogously to Example 58, using 0.3194 g (1.0944 mmol) Diphenhydramine·HCl in 100 ml ion-exchanged water (pH 6.39) and 100 ml 0.00125M dextransulphate-solution.

EXAMPLE 63

Imipramine salt of Dextran Sulphate 12000

Analogously to Example 58, using 0.3302 g (1.0421 mmol) Imipramine·HCl in 100 ml ion-exchanged water (pH 6.13) and 100 ml 0.00125M dextransulphate-solution.

Yield: 0.3727 g

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EXAMPLE 64

Nortriptyline salt of Dextran Sulphate 12000

Analogously to Example 58, using 0.1964 g (0.6550 mmol) Nortriptyline·HCl in 100 ml ion-exchanged water (pH 6.48) and 100 ml 0.00125M dextran sulphate-solution.

EXAMPLE 65

Propranolol salt of Dextran Sulphate 12000

Analogously to Example 58, using 0.3183 g (1.0761 mmol) Propranolol·HCl in 100 ml ion-exchanged water (pH 6.07) and 100 ml 0.00125M dextran sulphate-solution.

EXAMPLE 66

Quinidine salt of Dextran Sulphate 12000

Analogously to Example 58, using 0.8361 g (1.1194 mmol) Quinidine Sulphate in 300 ml ion-exchanged water (pH 6.43) and 100 ml 0.00125M dextran sulphate-solution.

EXAMPLE 67

Tobramycin salt of Dextran Sulphate 12000

Analogously to Example 58, using 0.4616 g (0.9873 mmol) Tobramycin in 100 ml ion-exchanged water (pH 10.29) and 100 ml 0.00125M dextran sulphate-solution.

EXAMPLE 68

Verapamil salt of Dextran Sulphate 12000

Analogously to Example 58, using 0.1858 g (0.3784 mmol) Verapamil·HCl in 100 ml ion-exchanged water (pH 6.18) and 100 ml 0.00125M dextran sulphate-solution.

Yield: 0.1805 g

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EXAMPLE 69

Bacitracin salt of Dextran Sulphate 12000

1,4489 g (1,0185 mmol) Bacitracin is dissolved in 1M HCl (pH 0.30) and by addition of 100 ml 0.00125M dextransulphate-solution, precipitation takes place. The reaction mixture is filtered and vacuum dried at 1Torr/25°C/20h/Sicapent°.

Yield: 0.5592 g

Example 70

Cinnarizine salt of Dextran Sulphate 12000

Analogously to Example 69, using 0.3697 g (1.0033 mmol) Cinnarizine in 100 ml 1M HCl (pH 0.02) and 100 ml 0.00125M dextransulphate-solution.

Yield: 0.2818 g

EXAMPLE 71

Desipramine salt of Dextran Sulphate 12000

Analogously to Example 69, using 0.2707 g (1.0163 mmol) Desipramine in 100 ml 1M HCl (pH 0.35) and 100 ml 0.00125M dextransulphate-solution.

Yield: 0.2624 g

EXAMPLE 72

Doxycyclin salt of Dextran Sulphate 12000

Analogously to Example 69, using 0.4631 g (1.0014 mmol) Doxycyclin Monohydrate in 100 ml 1M HCl (pH 0.08) and 100 ml 0.00125M dextransulphate-solution.

Yield: 0.1969 g

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EXAMPLE 73

Ergotamine salt of Dextran Sulphate 12000

Analogously to Example 69, using 1.2396 g (0.9439 mmol) Ergotamine Tartrate in 400 ml 1M HCl (pH 0.07) and 100 ml 0.00125M dextransulphate-solution.

Yield: 0.2300 g

EXAMPLE 74

Flunarizine salt of Dextran Sulphate 12000

Analogously to Example 69, using 0.1861 g (0.3898 mmol) Flunarizine 2HCl in 100 ml 1M HCl (pH 0.38) and 100 ml 0.00125M dextransulphate-solution.

EXAMPLE 75

Polymyxin salt of Dextran Sulphate 12000

Analogously to Example 69, using 1.2537 g (1.0448 mmol) Polymyxin in 100 ml 1M HCl (pH 0.15) and 100 ml 0.00125M dextransulphate-solution.

Yield: 0.7958 g

EXAMPLE 76

Vancomycin salt of Dextran Sulphate 12000

Analogously to Example 69, using 0.7578 g (0.5229 mmol) Vancomycin in 100 ml 1M HCl (pH 0.24) and 100 ml 0.00125M dextransulphate-solution.

EXAMPLE 77

Cyproheptadiene salt of Dextran Sulphate 12000

0.3600 g (1.0260 mmol) Cyproheptadiene HCl sesquihydrate is dissolved in 100 ml methanol (pH 4.74).

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The solution is adjusted to pH 4.00 with 1M HCl (pH 2.00). Addition of 100 ml 0.00125M dextransulphate-solution results in precipitation. The reaction mixture is filtered and vacuum dried at 1Torr/25°C/20h/Sicapent®.

Yield: 0.4833 g

EXAMPLE 78

Noscapine salt of Dextran Sulphate 120000

0.0311 g (0.06913 mmol) Noscapine·HCl is dissolved in 10 ml ion-exchanged water (pH 4.85) and by addition of 100 ml 0.00008333M Dextransulphate-solution (MW = 120000 g/mol), precipitation takes place.

EXAMPLE 79

Vancomycin salt of Dextran Sulphate 120000

Analogously to Example 78, using 0.1032 g (0.06946 mmol) Vancomycin·HCl in 10 ml ion-exchanged water (pH 3.69) and 100 ml 0.00008333M dextransulphate-solution.

EXAMPLE 80

Amitriptyline salt of Dextran Sulphate 120000

0.0231 g (0.07359 mmol) Amitriptyline·HCl is dissolved in 10 ml ion-exchanged water (pH 7.24). The solution is adjusted to pH 4.00 with 1M HCl (pH 2.82) and by addition of 100 ml 0.00008333M dextransulphate-solution, precipitation takes place.

EXAMPLE 81

Chlorpromazine salt of Dextran Sulphate 120000

Analogously to Example 80, using 0.0259 g (0.07288 mmol) Chlorpromazine·HCl in 10 ml ion-exchanged water (pH 6.61) and 100 ml 0.00008333M dextransulphate-solution.

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EXAMPLE 82

Cyclobenzaprine salt of Dextran Sulphate 120000

Analogously to Example 80, using 0.0213 g (0.06830 mmol) Cyclobenzaprine·HCl in 10 ml ion-exchanged water (pH 6.56) and 100 ml 0.00008333M dextran sulphate-solution.

EXAMPLE 83

Indomethacine salt of Dextran Sulphate 120000

Analogously to Example 80, using 0.0298 g (0.08328 mmol) Indomethacine in 10 ml ion-exchanged water (pH 5.47) and 100 ml 0.00008333M dextran sulphate-solution.

EXAMPLE 84

Quinidine salt of Dextran Sulphate 120000

Analogously to Example 80, using 0.0568 g (0.07604 mmol) Quinidine Sulphate in 10 ml ion-exchanged water (pH 6.98) and 100 ml 0.00008333M dextran sulphate-solution.

EXAMPLE 85

Tobramycin salt of Dextran Sulphate 120000

Analogously to Example 80, using 0.0416 g (0.08898 mmol) Tobramycin in 10 ml ion-exchanged water (pH 10.43) and 100 ml 0.00008333M dextran sulphate-solution.

EXAMPLE 86

Verapamil salt of Dextran Sulphate 120000

Analogously to Example 80, using 0.0346 g (0.07046 mmol) Verapamil·HCl in 10 ml ion-exchanged water (pH 7.00) and 100 ml 0.00008333M dextran sulphate-solution.

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EXAMPLE 87

Bacitracin salt of Dextran Sulphate 120000

0.0957 g (0.06727 mmol) Bacitracin is dissolved in 10 ml 1M HCl (pH 0.33) and by addition of 100 ml 0.00008333M dextran sulphate-solution, precipitation takes place.

EXAMPLE 88

Cinnarizine salt of Dextran Sulphate 120000

Analogously to Example 87, using 0.0260 g (0.07056 mmol) Cinnarizine in 10 ml 1M HCl (pH 0.76) and 100 ml 0.00008333M dextran sulphate-solution.

EXAMPLE 89

Polymyxin salt of Dextran Sulphate 120000

Analogously to Example 87, using 0.0806 g (0.06717 mmol) Polymyxin in 10 ml 1M HCl (pH 0.43) and 100 ml 0.00008333M dextran sulphate-solution.

EXAMPLE 90

Diclofenac salt of Dextran Sulphate 120000

0.0236 g (0.07418 mmol) Diclofenac-Na is dissolved in 10 ml ethanol (pH 8.63). The solution is adjusted to pH 4.00 with 1M HCl (pH 1.55) and by addition of 100 ml 0.00008333M dextran sulphate-solution, precipitation takes place.

EXAMPLE 91

Cyclobenzaprine salt of Dextran Phosphate 72000

0.0676 g (0.2168 mmol) Cyclobenzaprine-HCl is dissolved in 50 ml ion-exchanged water and by addition of 100 ml 0.0001389M Dextranphosphate-solution (MW =

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72000 g/mol), precipitation takes place. The reaction mixture is filtered and vacuum dried at 1Torr/25°C/20h/ Sicapent®.

EXAMPLE 92

Imipramine salt of Dextran Phosphate 72000

Analogously to Example 91, using 0.0829 g (0.2616 mmol) Imipramine·HCl in 50 ml ion-exchanged water and 100 ml 0.0001389M dextranphosphate-solution.

EXAMPLE 93

Noscapine salt of Dextran Phosphate 72000

Analogously to Example 91, using 0.0533 g (0.1185 mmol) Noscapine·HCl in 50 ml ion-exchanged water (pH 5.65) and 100 ml 0.0001389M dextranphosphate-solution.

Yield: 0.1733 g

EXAMPLE 94

Polymyxin salt of Dextran Phosphate 72000

0.3155 g (0.2629 mmol) Polymyxin is dissolved in 50 ml 1M HCl (pH 0.22) and by addition of 100 ml 0.0001389M dextranphosphate-solution, precipitation takes place.

EXAMPLE 95

Vancomycin salt of Dextran Phosphate 72000

Analogously to Example 94, using 0.3800 g (0.2622 mmol) Vancomycin in 50 ml 1M HCl (pH 1.13) and 100 ml 0.0001389M dextranphosphate-solution.

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EXAMPLE 96

Amitriptyline salt of Phytic Acid

2.0466 g (6.5201 mmol) Amitriptyline·HCl is dissolved in 100 ml ion-exchanged water (pH 3.89) and by addition of 100 ml 0.01082M Phytic acid, precipitation takes place. The reaction mixture is filtered and vacuum dried at 1Torr/25°C/20h/Sicapent®.

EXAMPLE 97

Chlordiazepoxid salt of Phytic Acid

Analogously to Example 96, using 2.1999 g (6.5419 mmol) Chlordiazepoxid·HCl in 200 ml ion-exchanged water (pH 3.34) and 100 ml 0.01082M phytic acid.

Yield: 1.2698 g

EXAMPLE 98

Chlorpromazine salt of Phytic Acid

Analogously to Example 96, using 2.3396 g (6.5832 mmol) Chlorpromazine·HCl in 100 ml ion-exchanged water (pH 4.84) and 100 ml 0.01082M phytic acid.

Yield: 0.9340 g

EXAMPLE 99

Cyclobenzaprine salt of Phytic Acid

Analogously to Example 96, using 2.0401 g (6.5421 mmol) Cyclobenzaprine·HCl in 100 ml ion-exchanged water (pH 4.54) and 100 ml 0.01082M phytic acid.

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EXAMPLE 100

Diltiazem salt of Phytic Acid

Analogously to Example 96, using 2.9578 g (6.5586 mmol) Diltiazem·HCl in 100 ml ion-exchanged water (pH 4.84) and 100 ml 0.01082M phytic acid.

Yield: 1.5777 g

EXAMPLE 101

Noscapine salt of Phytic Acid

Analogously to Example 96, using 2.9277 g (6.5083 mmol) Noscapine·HCl in 100 ml ion-exchanged water (pH 4.46) and 100 ml 0.01082M phytic acid.

Yield: 2.4057 g

EXAMPLE 102

Vancomycin salt of Phytic Acid

Analogously to Example 96, using 9.6587 g (6.5008 mmol) Vancomycin·HCl in 200 ml ion-exchanged water (pH 3.64) and 100 ml 0.01082M phytic acid.

Yield: 6.4126 g

EXAMPLE 103

Diphenhydramine salt of Phytic Acid

1.8906 g (6.4780 mmol) Diphenhydramine·HCl is dissolved in 100 ml ion-exchanged water (pH 6.11). The solution is adjusted to pH 4.00 with 1M HCl (pH 4.01) and by addition of 100 ml 0.01082M phytic acid, precipitation takes place. The reaction mixture is filtered and vacuum dried at 1Torr/25°C/20h/Sicapent®.

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EXAMPLE 104

Quinidine salt of Phytic Acid

Analogously to Example 103, using 4.8460 g (6.4879 mmol) Quinidine Sulphate in 600 ml ion-exchanged water (pH 6.68) and 100 ml 0.01082M phytic acid.

Yield: 1.4377 g

EXAMPLE 105

Tobramycin salt of Phytic Acid

Analogously to Example 103, using 3.0606 g (6.5462 mmol) Tobramycin in 100 ml ion-exchanged water (pH 10.51) and 100 ml 0.01082M phytic acid.

Yield: 0.9609 g

EXAMPLE 106

Verapamil salt of Phytic Acid

Analogously to Example 103, using 3.1870 g (6.4903 mmol) Verapamil-HCl in 200 ml ion-exchanged water (pH 6.90) and 100 ml 0.01082M phytic acid.

EXAMPLES 107 to 119

Formation of aqueous sparingly soluble dextran-drug complexes

The experiments were carried out in aqueous solutions, and the precipitations were generally performed at pH

4 - 6.

Three different derivatives of dextran were used : dextran phosphate ($M_{wt} = 72000$, P : 14 %); dextran sulphate ($M_{wt} = 12000$, S : 17 %); dextran sulphate ($M_{wt} = 120000$, S : 14,2 %). The derivatives were obtained from

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Pharmacia, Biotech, Sweden.

To obtain a complete binding of drug to all sulphur/phosphorus oxyacid-groups on the dextran molecule, the amount of drug added to the dextran solution had to be at least equimolar to the amount of sulphur/phosphorus bound to the dextran molecules.

The desired concentration of dextran in the final mixed solution was 10 g/l for dextran phosphate and 5 g/l for the dextran sulphates.

For i.e dextran phosphate ($M_{wt} = 72000$, P : 14 %), the following equation was used:

Final volume of solution : 6 ml. ~ 60 mg dextran phosphate

60 mg dextran phosphate = $60 * 0.14$ mg phosphate = 8.4 mg phosphate

= $0.0084/30.97$ mol phosphate = $2.7 * 10^{-4}$ mol phosphate

Amount drug to be added : $2.7 * 10^{-4} * M_{wt} (\text{drug})$ g

Similar calculations were made for the two dextran sulphates.

Procedure for precipitation of drugs with dextran phosphate and results :

A standard-solution of dextran phosphate (20 g/l) was prepared.

The calculated amount of drug was dissolved in 3 ml of distilled water. In case of sparingly soluble drugs, pH was adjusted to 1-3 with 2 M HCl, to get the basic drugs on salt-form. Then 3 ml of the dextran solution was added. If no precipitation was observed, the pH of the solution was varied between 1-8 to see if the complex-formation/precipitation was pH-dependent.

The precipitate was separated, either by filtration through G3 glassfilters, or if the complex was very fine, by centrifugation and subsequent decantation of the solvent.

To confirm the dextran-drug complex formation, DSC

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analyses were performed.

Experimental results of complex formation with dextran phosphate ($M_{wt} = 72000$, P : 14 %):

Drug	Precipitation	Example No.	DSC
Cyclobenzaprine ($M_{wt} = 257.4$)	yes	107	confirmed
Polymyxin ($M_{wt} = 1202$)	yes	108	
Imipramine ($M_{wt} = 315.4$)	yes	109	-

Procedure for precipitation of dextran sulphates and results:

A standard-solution of dextran sulphate (10 g/l) was prepared.

The calculated amount of drug was dissolved in 10 ml of distilled water. In case of sparingly soluble drugs, pH was adjusted to 1-3 with 1 M HCl, to get the basic drugs on salt-form. Then 10 ml of the dextran solution was added. If no precipitation was observed and the pH was different from 4-5, the pH of the solution was adjusted to this value.

The precipitate was separated, by centrifugation and subsequent decantation of the solvent.

To confirm the dextran-drug complex formation, DSC analyses were performed.

Experimental result of complex-formation with dextran sulphate ($M_{wt} = 120000$, S : 14,2 %):

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Drug	Precipitation	Example No.	DSC
Cyclobenzaprine ($M_{wt} = 257.4$)	yes	110	
Bacitracin ($M_{wt} = 1421$)	yes	111	Confirmed
Polymyxin ($M_{wt} = 1202$)	yes	112	
Vancomycin ($M_{wt} = 1449$)	yes	113	-
Imipramine ($M_{wt} = 315.4$)	yes	114	
Quinidine ($M_{wt} = 324.4$)	yes	115	Confirmed
Ergotamine ($M_{wt} = 581.7$)	yes	116	

Experimental results of complex formation with dextran sulphate ($M_{wt} = 12000$, S : 17 %) :

Drug	Precipitation	Example No.	DSC
Cyclobenzaprine ($M_{wt} = 257.4$)	yes	117	-
Polymyxin ($M_{wt} = 1202$)	yes	118	Confirmed
Bacitracin ($M_{wt} = 1421$)	yes	119	-

EXAMPLE 120

Analysis of sucrose-octa-O-sulphonic acid salts

The following drug substances and the Sucrose-octa-O-sulphonic acid salts of these substances were analysed as described below.

The Sucrose-octa-O-sulphonic acid salt of the

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active substance was dissolved in a 1% sodium chloride solution and analysed by HPLC, using the parameters below:

Mobile phase: Ammonium sulphate solution in water,
132mg/ml.

Detection: Refractive index detector.

Column: 5% phenyl 95% methylpolysilane chemically bound to silica gel, 3.9mm x 30cm.

The content of the active substances was measured by UV when possible, at a suitable UV_{max} of the active substance.

The Sucrose-octa-O-sulphonic acid salt of the active substance was analysed by DSC. The melting point or destruction point of the active substance was determined. The destruction temperature of the Sucrose-octa-O-sulphonic acid salt of the substance was found, and it was shown that the melting or destruction temperature of the active substance could not be recognized in the Sucrose-octa-O-sulphonic acid salt. Additionally it was shown that the destruction temperature of Sucrose-octa-O-sulphonic acid sodium salt was different from the destruction temperature of the Sucrose-octa-O-sulphonic acid salt of the active substances.

Sucrose-octa-O-sulphonic acid sodium salt itself has a destruction temperature of about 125°C.

Bacitracin-SOS:

Bacitracin: Not analysed, due to no chromophoric groups being present.

DSC: The Sucrose-octa-O-sulphonic acid salt of bacitracin has no melting point, but starts to decompose at about 150°C. The destruction temperature of Sucrose-

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octa-O-sulphonic acid sodium salt is about 125°C, this indicates that Sucrose-octa-O-sulphonic acid and bacitracin precipitate as a salt.

Cyclobenzaprine-SOS:

Cyclobenzaprine: 32% calculated with reference to the non-dried substance.

DSC: Melting point of cyclobenzaprine was found to be 214.9°C.

The Sucrose-octa-O-sulphonic acid salt of cyclobenzaprine has no melting point, but the substance starts to decompose at about 200°C.

No endotherm was seen at 214.9°C, showing that cyclobenzaprine was not present as crystals in the mixture.

This indicates that Sucrose-octa-O-sulphonic acid and cyclobenzaprine precipitate as a salt.

Diltiazem-SOS:

Diltiazem: 79% calculated with reference to the non-dried substance.

DSC: Melting point of diltiazem was found to be 207.6°C.

The Sucrose-octa-O-sulphonic acid salt of diltiazem has no melting point, but the substance starts to decompose at 170°C.

No endotherm was seen at 207.6°C, showing that diltiazem was not present as crystals in the mixture.

This indicates that Sucrose-octa-O-sulphonic acid and diltiazem precipitate as a salt.

Water: 3.9%

Erythromycin-SOS:

Erythromycin: Not analysed, due to no chromophoric groups being present.

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DSC: Erythromycin hydrated crystals melt at 135-140°C, resolidify and melt again at 190-193°C.

The Sucrose-octa-O-sulphonic acid salt of erythromycin has no melting point, but the substance starts to decompose at 200°C.

A small exotherm and endotherm is seen at 130-140°C showing that a small amount of erythromycin might be present as crystals in the salt. However, most of the erythromycin is not present as crystals in the mixture. This indicates that Sucrose-octa-O-sulphonic acid and erythromycin precipitate as a salt.

Nortriptyline-SOS:

SOS: 38% calculated with reference to the non-dried substance.

Nortriptyline: 43% calculated with reference to the non-dried substance.

DSC: Melting point of nortriptyline was found to be 213.3°C.

The Sucrose-octa-O-sulphonic acid salt of nortriptyline has no melting point, but starts to decompose at 190°C.

No endotherm was seen at 213.3°C, showing that nortriptyline was not present as crystals in the mixture.

This indicates that Sucrose-octa-O-sulphonic acid and nortriptyline precipitate as a salt.

Noscapine-SOS:

Noscapine: 87% calculated with reference to the non-dried substance.

DSC: Melting point of noscapine was found to be 203.7°C.

The Sucrose-octa-O-sulphonic acid salt of noscapine has no melting point, but starts to decompose at 200°C.

No endotherm was seen at 203.7°C, showing that noscapine was not present as crystals in the mixture.

This indicates that Sucrose-octa-O-sulphonic acid and

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noscapine precipitate as a salt.

Polymyxin-SOS:

SOS: 37.8% calculated with reference to the non-dried substance.

Polymyxin: Not analysed, due to no chromophoric groups being present.

DSC: Polymyxin starts to decompose at 125°C.

The Sucrose-octa-O-sulphonic acid salt of polymyxin has no melting point, but does not start to decompose before 160°C.

This indicates that polymyxin is not present as crystals in the mixture and that Sucrose-octa-O-sulphonic acid and polymyxin precipitate as a salt.

Quinidine-SOS:

SOS: 39%

Quinidine: 69%

DSC: Quinidine melts at 170°C, recrystallizes and melts again at 180°C.

The Sucrose-octa-O-sulphonic acid salt of quinidine has no melting point, but starts to decompose at 175°C.

No endotherm was seen at 170 or 180°C, showing that quinidine was not present as crystals in the mixture.

This indicates that Sucrose-octa-O-sulphonic acid and quinidine precipitate as a salt.

Vancomycin-SOS:

Vancomycin: Not analysed, due to no chromophoric groups being present.

DSC: Vancomycin starts to decompose at 125°C.

The Sucrose-octa-O-sulphonic acid salt of vancomycin has no melting point, but does not start to decompose before 135°C.

This indicates that vancomycin is not present as

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crystals in the mixture and that Sucrose-octa-O-sulphonic acid and vancomycin precipitate as a salt.

Verapamil-SOS:

Verapamil: 93% calculated with reference to the non-dried substance.

DSC: Melting point of verapamil was found to be 141.2°C. The Sucrose-octa-O-sulphonic acid salt of verapamili has no melting point, but starts to decompose instead. No endotherm was seen at 141.2°C, showing that verapamil was not present as crystals in the mixture. This indicates that verapamil is not present as crystals in the mixture and that Sucrose-octa-O-sulphonic acid and verapamil precipitate as a salt.

Benztropine-SOS:

SOS: 19.1 % calculated with reference to the non-dried substance.

Benztropine: 54 % calculated with reference to the non-dried substance.

EXAMPLE 121

Analysis of dextran phosphate salts

The drug substance and the dextran phosphate salt of the substance were analysed as described below.

The dextran phosphate salt of the active substance was analysed by DSC. The melting point or destruction point of the active substance was determined. The destruction temperature of the dextran phosphate salt of the substance was found, and it was shown that the melting or destruction temperature of the active substance could not be recognized in the dextran phosphate salt. Additionally it was shown that the destruction temperature of dextran phosphate was

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different from the destruction temperature of the dextran phosphate salt of the active substance.

Dextran phosphate has a destruction temperature of about 130-140°C.

Cyclobenzaprine-dextran phosphate:

DSC: Melting point of cyclobenzaprine was found to be 214.9°C.

The dextran phosphate salt of cyclobenzaprine has no melting point, but the substance starts to decompose at 125°C.

This indicates that the active substance is not present as crystals in the mixture and that dextran phosphate and cyclobenzaprine precipitate as a salt.

Polymyxin-dextran phosphate (pH 9):

DSC: Polymyxin has no melting point but starts to decompose at 125°C.

The dextran phosphate salt of polymyxin has no melting point, but the substance starts to decompose at 135°C. This indicates that the active substance is not present as crystals in the mixture and that dextran phosphate and polymyxin precipitate as a salt.

Polymyxin-dextran phosphate (pH 5):

DSC: Polymyxin has no melting point but starts to decompose at 125°C.

The dextran phosphate salt of polymyxin has no melting point, but the substance starts to decompose at 140°C. This indicates that the active substance is not present as crystals in the mixture and that dextran phosphate and polymyxin precipitate as a salt.

EXAMPLE 122

Analysis of dextran sulphate 120000 salts

The drug substances and the dextran sulphate salts

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of these substances, were analysed as described below.

The dextran sulphate salt of the active substance was analysed by DSC. The melting point or destruction point of the active substance was determined. The destruction temperature of the dextran sulphate salt of the substance was found, and it was shown that the melting or destruction temperature of the active substance could not be recognized in the dextran sulphate salt. Additionally it was shown that the destruction temperature of dextran sulphate was different from the destruction temperature of the dextran sulphate salt of the active substances.

Dextran sulphate 120 000 has a destruction temperature of about 150°C.

Bacitracin-dextran sulphate (120kD):

DSC: The dextran sulphate salt of bacitracin has no melting point, but starts to decompose at 125°C. The destruction temperature of dextran sulphate is 150°C. This indicates that dextran sulphate and bacitracin precipitate as a salt.

Quinidine-dextran sulphate (120kD):

DSC: Quinidine melts at about 170°C, recrystallizes and melts again at 180°C. The dextran sulphate salt of quinidine has no melting point, but starts to decompose at 140°C. This indicates that quinidine is not present as crystals in the mixture and that dextran sulphate and quinidine precipitate as a salt.

Ergotamine-dextran sulphate (120kD):

DSC: Ergotamine has a destruction temperature at 212 - 214°C. A clear endotherm is seen at 125°C, which resembles a melting. At temperatures above 125°C, a destruction develops. No definitive conclusion can be

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drawn from the thermogram.

Vancomycin-dextran sulphate (120kD) :

DSC: Vancomycin starts to decompose at 125°C. The dextran sulphate salt of vancomycin has no melting point, but does not start to decompose before 140°C. This indicates, that vancomycin is not present as crystals in the mixture and that dextran sulphate and vancomycin precipitate as a salt.

EXAMPLE 123

Analysis of dextran sulphate 12000 salts

The drug substance and the dextran sulphate salt of the substance were analysed as follows.

The dextran sulphate salt of the active substance was analysed by DSC. The melting point or destruction point of the active substance was determined. The destruction temperature of the dextran sulphate salt of the substance was found, and it was shown that the melting or destruction temperature of the active substance could not be recognized in the dextran sulphate salt. Additionally it was shown that the destruction temperature of dextran sulphate was different from the destruction temperature of the dextran sulphate salt of the active substance.

Dextran sulphate 12 000 has a destruction temperature of 150°C.

Polymyxin-dextran sulphate (12kD) :

DSC: Polymyxin starts to decompose at 125°C. The dextran sulphate salt of polymyxin has no melting point, but does not start to decompose before 140°C. This indicates that polymyxin is not present as crystals in the mixture and that dextran sulphate and polymyxin precipitate as a salt.

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Cyclobenzaprine-dextran sulphate (12kD):

The content of cyclobenzaprine in the salt was found to be 57 %.

UV: Comparing the UV profile of cyclobenzaprine dextran sulphate with the UV profile of cyclobenzaprine it was concluded that cyclobenzaprine is a component of the salt (dextran sulphate 12000 has only negligible absorbance).

IR: The infrared absorption spectra of cyclobenzaprine, dextran sulphate 12000 and cyclobenzaprine dextran sulphate indicate that cyclobenzaprine and dextran sulphate are present in the salt. No difference is seen, comparing dextran sulphate 5000 to dextran sulphate 12000.

DSC: The melting point of cyclobenzaprine was found to be 214.9°C.

The dextran sulphate salt of cyclobenzaprine has no melting point, but starts to decompose at 160°C. The destruction point of dextran sulphate is 130-150°C and the melting point of cyclobenzaprine expected at 215°C is absent.

This indicates that dextran sulphate and cyclobenzaprine precipitate as a salt.

Doxycyclin-dextran sulphate (12kD):

The content of doxycycline in the salt was found to be 56 %.

UV: Comparing the UV profile of doxycycline dextran sulphate with the UV profile of doxycycline it was concluded that doxycycline is a component of the salt (dextran sulphate 12000 has only negligible

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absorbance).

IR: The infrared absorption spectra of doxycycline, dextransulphate 12000 and doxycycline dextransulphate indicate that doxycycline and dextransulphate are present in the salt. No difference is seen, comparing dextransulphate 5000 to dextransulphate 12000.

DSC: The dextransulphate salt of doxycycline has no melting point, but starts to decompose at 130°C. The destruction point of dextransulphate 12000 is 130-150°C, so the decomposition in the salt starts at a lower temperature, than in the dextransulphate.

Benztropine-dextransulphate (12kD):

The content of benztrpine in the salt was found to be 73 %.

UV: Comparing the UV profile of benztrpine dextransulphate with the UV profile of benztrpine it was concluded that benztrpine is a component of the salt (dextransulphate 12000 has only negligible absorbance).

IR: The infrared absorption spectra of benztrpine, dextransulphate 12000 and benztrpine dextransulphate indicate that benztrpine and dextransulphate are present in the salt. No difference is seen, comparing dextransulphate 5000 to dextransulphate 12000.

DSC: The dextransulphate salt of benztrpine has no melting point, but starts to decompose at 180-190°C. The destruction point of dextransulphate is 130-150°C, and the melting point of benztrpine mesylate at 143°C is absent as well. This indicates that dextransulphate 12000 and benztrpine precipitate as a salt.

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Diltiazem-dextransulphate (12kD):

The content of diltiazem in the salt was found to be 72 %.

UV: Comparing the UV profile of diltiazem dextransulphate with the UV profile of diltiazem it was concluded that diltiazem is a component of the salt (dextransulphate 12000 has only negligible absorbance).

IR: The infrared absorption spectra of diltiazem, dextransulphate 12000 and diltiazem dextransulphate indicate that diltiazem and dextransulphate are present in the salt. No difference is seen, comparing dextransulphate 5000 to dextransulphate 12000.

DSC: In the thermogram of diltiazem dextransulphate 12000 an exotherm/endotherm is seen at 180°C. The destruction point of dextransulphate 12000 at 130-150°C is absent. Diltiazem has a destruction point of about 187- 188°C, but in the thermogram no endotherm is detected which corresponds to the decomposition of diltiazem, indicating that dextransulphate and diltazem precipitate as a salt.

Imipramine-dextransulphate (12kD):

The content of imipramine in the salt was found to be 73 %.

UV: Comparing the UV profile of imipramine dextransulphate with the UV profile of imipramine it was concluded that imipramine is a component of the salt (dextransulphate 12000 has only negligible absorbance).

IR: The infrared absorption spectra of imipramine, dextransulphate 12000 and imipramine dextransulphate

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indicate that imipramine and dextransulphate are present in the salt. No difference is seen, comparing dextransulphate 5000 to dextransulphate 12000.

DSC: The dextransulphate salt of imipramine has no melting point, but starts to decompose at 180-190°C. The destruction point of dextransulphate 12000 is 130-150°C, and the destruction point of imipramine at 160°C is absent. This indicates that dextransulphate 12000 and imipramine precipitate as a salt.

Cinnarizine-dextransulphate (12kD):

The content of cinnarizine in the salt was found to be 91 %.

UV: Comparing the UV profile of cinnarizine dextransulphate with the UV profile of cinnarizine it was concluded that cinnarizine is a component of the salt (dextransulphate 12000 has only negligible absorbance).

DSC: The dextransulphate salt of cinnarizine has no melting point, but has a reproducible series of endotherms. The destruction point of dextransulphate 12000 at 150°C is absent. An endotherm is seen at 190°C (while the destruction point of cinnarizine HCl is expected at 192°C), although this is a very sharp endotherm and thus does not have the appearance normally associated with a decomposition. This indicates that dextransulphate 12000 and cinnarizine precipitate as a salt.

EXAMPLE 124

Analysis of dextran sulphate 5000 salts

The drug substances and the dextran sulphate salts

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of those substances were analysed as described in Examples 122 and 123.

Dextransulphate 5000 starts to decompose at a temperature of 125-130°C.

Doxycycline-dextransulphate (5kD):

The content of doxycycline in the salt was found to be 83 %.

UV: Comparing the UV profile of doxycycline dextransulphate with that of doxycycline it was concluded that doxycycline is one of the components of the salt (dextransulphate 5000 has only negligible absorbance).

IR: The infrared absorption spectra of doxycycline, dextransulphate 5000 and doxycycline dextransulphate indicate that doxycycline and dextransulphate are present in the salt. No difference is seen, comparing dextransulphate 5000 to dextransulphate 12000.

DSC: The dextransulphate salt of doxycycline has no melting point, but starts to decompose at 210°C. The destruction point of dextransulphate 5000 at 125-130° and the destruction point of doxycycline at 175°C are absent. This indicates that dextransulphate 5000 and doxycycline precipitate as a salt.

Cyclobenzaprine-dextransulphate (5kD):

The content of cyclobenzaprine in the salt was found to be 73 %.

UV: Comparing the UV profile of cyclobenzaprine dextransulphate with the UV profile of cyclobenzaprine it was concluded that cyclobenzaprine is a component of

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the salt (dextransulphate 5000 has only negligible absorbance).

IR: The infrared absorption spectra of cyclobenzaprine, dextransulphate 5000 and cyclobenzaprine dextransulphate indicate that cyclobenzaprine and dextransulphate are present in the salt. No difference is seen, comparing dextransulphate 5000 to dextransulphate 12000.

DSC: The dextransulphate salt of cyclobenzaprine has no melting point, but starts to decompose at 180°C. The destruction point of dextransulphate 5000 at 125-130°C, and the melting point of cyclobenzaprine expected at 215°C are absent. This indicates that dextransulphate 5000 and cyclobenzaprine precipitate as a salt.

Benztropine-dextransulphate (5kD):

The content of benzotropine in the salt was found to be 73 %.

UV: Comparing the UV profile of benzotropine dextransulphate with the UV profile of benzotropine it was concluded that benzotropine is a component of the salt (dextransulphate 5000 has only negligible absorbance).

IR: The infrared absorption spectra of benzotropine, dextransulphate 5000 and benzotropine dextransulphate indicate that benzotropine and dextransulphate are present in the salt. No difference is seen, comparing dextransulphate 5000 to dextransulphate 12000.

DSC: The dextransulphate salt of benzotropine has no melting point, but starts to decompose at 180-190°C. The destruction point of dextransulphate 5000 is 125-130°C, and the melting point of benzotropine mesylate at 143°C

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is absent. This indicates that dextransulphate 5000 and benztropine precipitate as a salt.

Diltiazem-dextransulphate (5kD):

The content of diltiazem in the salt was found to be 77 %.

UV: Comparing the UV profile of diltiazem dextransulphate with the UV profile of diltiazem it was concluded that diltiazem is a component of the salt (dextransulphate 5000 has only negligible absorbance).

IR: The infrared absorption spectra of diltiazem, dextransulphate 5000 and diltiazem dextransulphate indicate that diltiazem and dextransulphate are present in the salt. No difference is seen, comparing dextransulphate 5000 to dextransulphate 12000.

DSC: The dextransulphate salt of diltiazem has no melting point, but starts to decompose at 165°C. The destruction point of dextransulphate is 125-130°C, and the destruction point of diltiazem at 187 - 188°C is not detected. This indicates that dextransulphate 5000 and diltiazem precipitate as a salt.

Imipramine-dextransulphate (5kD):

The content of imipramine in the salt was found to be 78 %.

UV: Comparing the UV profile of imipramine dextransulphate with the UV profile of imipramine it was concluded that imipramine is a component of the salt (dextransulphate 5000 has only negligible absorbance).

IR: The infrared absorption spectra of imipramine, dextransulphate 5000 and imipramine dextransulphate

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indicate that imipramine and dextransulphate are present in the salt. No difference is seen, comparing dextransulphate 5000 to dextransulphate 12000.

DSC: The dextransulphate salt of imipramine has no melting point, but starts to decompose at 205°C. The destruction point of dextransulphate 5000 at 125-130°C, and the destruction point of imipramine at 160°C is absent. This indicates that dextransulphate 5000 and imipramine precipitate as a salt.

EXAMPLE 125

Analysis of Phytic acid salts

The drug substance and the phytic acid salt of the substance were analysed as described in Examples 120-124.

Diltiazem-phytic acid:

The content of diltiazem in the salt was found to be 82 %.

UV: Comparing the UV profile of diltiazem phytic acid with that of diltiazem it was concluded that diltiazem is one of the components of the salt (phytic acid has only negligible absorbance).

IR: The infrared absorption spectra of diltiazem, phytic acid and diltiazem phytic acid indicate that diltiazem and phytic acid are present in the salt.

DSC: In the thermogram of diltiazem phytic acid the decomposition starts at 200°C. The destruction point of phytic acid 125-130°C, and the destruction point of diltiazem at 187-188°C is absent. This indicates that phytic acid and diltiazem precipitate as a salt.

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Quinidine-phytic acid:

The content of quinidine in the salt was found to be 75 %.

UV: Comparing the UV profile of quinidine phytic acid with that of quinidine it was concluded that quinidine is one of the components of the salt (phytic acid has only negligible absorbance).

IR: The infrared absorption spectra of quinidine, phytic acid and quinidine phytic acid indicate that quinidine is present in the salt.

DSC: In the thermogram of quinidine phytic acid the decomposition starts at 140°C. The destruction point of phytic acid 125-130°C, and the destruction point of quinidine expected at 177°C is absent. This indicates that phytic acid and quinidine precipitate as a salt.

Noscapine-phytic acid:

The content of noscapine in the salt was found to be 84 %.

UV: Comparing the UV profile of noscapine phytic acid with that of noscapine it was concluded that noscapine is one of the components of the salt (phytic acid has only negligible absorbance).

IR: The infrared absorption spectra of noscapine, phytic acid and noscapine phytic acid indicate that noscapine is present in the salt.

DSC: In the thermogram of noscapine phytic acid, melting of noscapine is seen at 175°C. (Expected melting point of noscapine is 176°C). The substance starts to

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decompose at 180-190°C.

Chlordiazepoxide-phytic acid:

The content of chlordiazepoxide in the salt was found to be 94 %.

UV: Comparing the UV profile of chlordiazepoxide phytic acid with that of chlordiazepoxide it was concluded that chlordiazepoxide is one of the components of the salt (phytic acid has only negligible absorbance).

IR: The infrared absorption spectra of chlordiazepoxide, phytic acid and chlordiazepoxide phytic acid indicate that chlordiazepoxide is present in the salt.

DSC: In the thermogram of the chlordiazepoxide phytic acid salt, decomposition starts at 200°C. Expected melting point of chlordiazepoxide HCl is 213°C. The destruction point of phytic acid at 125-130°C and the melting endotherm of chlordiazepoxide are absent. This indicates that phytic acid and chlordiazepoxide precipitate as a salt.

EXAMPLE 126

Investigation of Oesophageal Irritation in the Cat

The ulcerogenic properties of drugs such as doxycycline are well documented (see for example Delphre et al. *Digestive Diseases and Sciences* 34: 797-800 (1989)).

The following test was carried out to compare the local ulcerogenic effects of doxycycline in four different administration forms.

Four groups, each of 4 cats, received doxycycline carageenate, doxycycline monohydrate, doxycycline

hyclate and doxycycline sucrose octasulfate, respectively (one tablet/cat).

The animals were anaesthetized and the tablet was placed in the oesophagus approximately 5 cm below the upper sphincter. The mucosa was inspected for lesions, immediately before and after the administration of the tablet, using an endoscope.

The animals were kept constantly anaesthetized and were killed 8 hours after tablet administration.

The oesophagus was exposed and external aspects were inspected. The oesophagus was opened in situ, the mucosa inspected and photographed.

The degree of disintegration of the tablets and any changes of the oesophagus were noted.

Two samples of oesophagus were collected, one from the site of tablet and one anterior to the site of tablet. The samples were prepared for histologic examination. The microscopic changes were recorded.

None of the tablets were completely disintegrated. The doxycycline monohydrate tablets were almost intact, the doxycycline carageenate tablets were disintegrated to an intermediate stage, whereas the doxycycline hyclate and doxycycline sucrose-octasulfate tablets were mostly disintegrated.

As the only macroscopic finding, a dry area was observed on the oesophageal mucosa in five cats.

Microscopically no changes were seen in the sample taken anterior to the site of the tablet. In the sample from the site of tablet from cats receiving doxycycline monohydrate or doxycycline sucrose octasulfate, no changes were observed.

In one cat receiving doxycycline carageenate, thinning of epithelium characterised by desquamation of outer layer and slight focal subepithelial and epithelial accumulation of primary neutrophils were observed.

In all four cats receiving doxycycline hyclate,

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moderate swelling and vacuolation of epithelial cells were observed. The basal layer remained intact in two of the cats whereas in the other two the vacuolation was present in the cells of the basal layer as well. Minimal focal epithelial accumulation of neutrophils was found in one cat.

This test showed that doxycycline monohydrate and doxycycline sucrose octasulfate tablets did not cause any damage to the oesophageal mucosa whereas minor lesions were seen in one out of four cats receiving doxycycline carageenate and four of four cats receiving doxycycline hyclate.

CLAIMS:

1. A therapeutic compound being a sugar acid salt of a biologically active organic compound, other than a sucrose-octa-O-sulphonic acid salt of an aminoglycoside.
2. A compound as claimed in claim 1 which is insoluble or poorly soluble in deionized water.
3. A compound as claimed in either of the preceding claims wherein said acid is a mono, di or oligosaccharide poly-O-sulphonic acid.
4. A compound as claimed in any one of the preceding claims wherein said acid is a disaccharide poly-O-sulphonic acid.
5. A compound as claimed in any one of the preceding claims wherein said compound is sucrose-octa-O-sulphonic acid.
6. A compound as claimed in any one of the preceding claims further containing a physiologically tolerable counterion.
7. A compound as claimed in claim 6 wherein said counterion is selected from alkali metal, alkaline earth metal, ammonium and aluminium ions.
8. A compound as claimed in claim 7 wherein said counterion is an aluminium ion.
9. A compound as claimed in any one of the preceding claims wherein said organic compound is a basic nitrogen atom containing compound.

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10. A compound as claimed in claim 9 wherein said organic compound contains a plurality of protonatable nitrogen atoms.

11. A compound as claimed in any one of the preceding claims wherein said organic compound is selected from the group consisting of antibacterials, antivirals, antimycotics, anti-amoebics, antiallergics, cardioprotectives, analgesics, anxiolytics, sedatives, hypnotics, anti-migraine agents, anti-motion sickness agents, anti-emetics, adrenergics, antispasmodics, muscle relaxants, neuroleptics, antidepressants, anticholinergics, antihistamines, anti-anorexics, and alkaloids.

12. A compound as claimed in any one of the preceding claims wherein said organic compound is an antibacterial.

13. A compound as claimed in claim 12 wherein said organic compound is an aminoglycoside, a tetracyclin, a polypeptide, a glycopeptide or a macrolide.

14. A compound as claimed in claim 12 wherein said organic compound is a tetracyclin.

15. A compound as claimed in claim 12 wherein said organic compound is selected from the group consisting of doxycyclin, diltiazam, cyclobenzaprine, bacitracin, noscapine, erythromycin, polymyxin, vancomycin, nortriptyline, quinidine, ergotamine, benztrapine, verapamil, flunarizine and imipramine,

16. A compound as claimed in claim 1 wherein said organic compound is selected from pindolol, diclofenac, desipramine amitriptyline, chlordiazepoxid, chlorpromazine, diphenhydramine, tobramycin,

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cinnarizine, furosemide, cyproheptadiene, carbamazepine, indomethacine and propranolol.

17. A compound as claimed in any one of claims 14 to 16 being a sucrose-octa-O-sulphonic acid salt of a said organic compound.

18. A compound as claimed in any one of claims 1 to 16 wherein said acid is a polysaccharide poly-O-sulphonic acid.

19. A compound as claimed in any one of claims 1 to 17 wherein said acid is a mono, di or oligosaccharide polysulphonic or polyphosphonic acid.

20. A compound as claimed in claim 1 being the sucrose-octa-O-sulphonic acid salt of doxycyclin.

21. A compound as claimed in any one of claims 1 to 20 for use as a therapeutic agent.

22. A pharmaceutical composition comprising a biologically active organic compound together with at least one physiologically acceptable carrier or excipient, characterized in that said compound, which is other than a sucrose-octa-O-sulphonic acid salt of an aminoglycoside, is present in the form of a salt with a sugar acid.

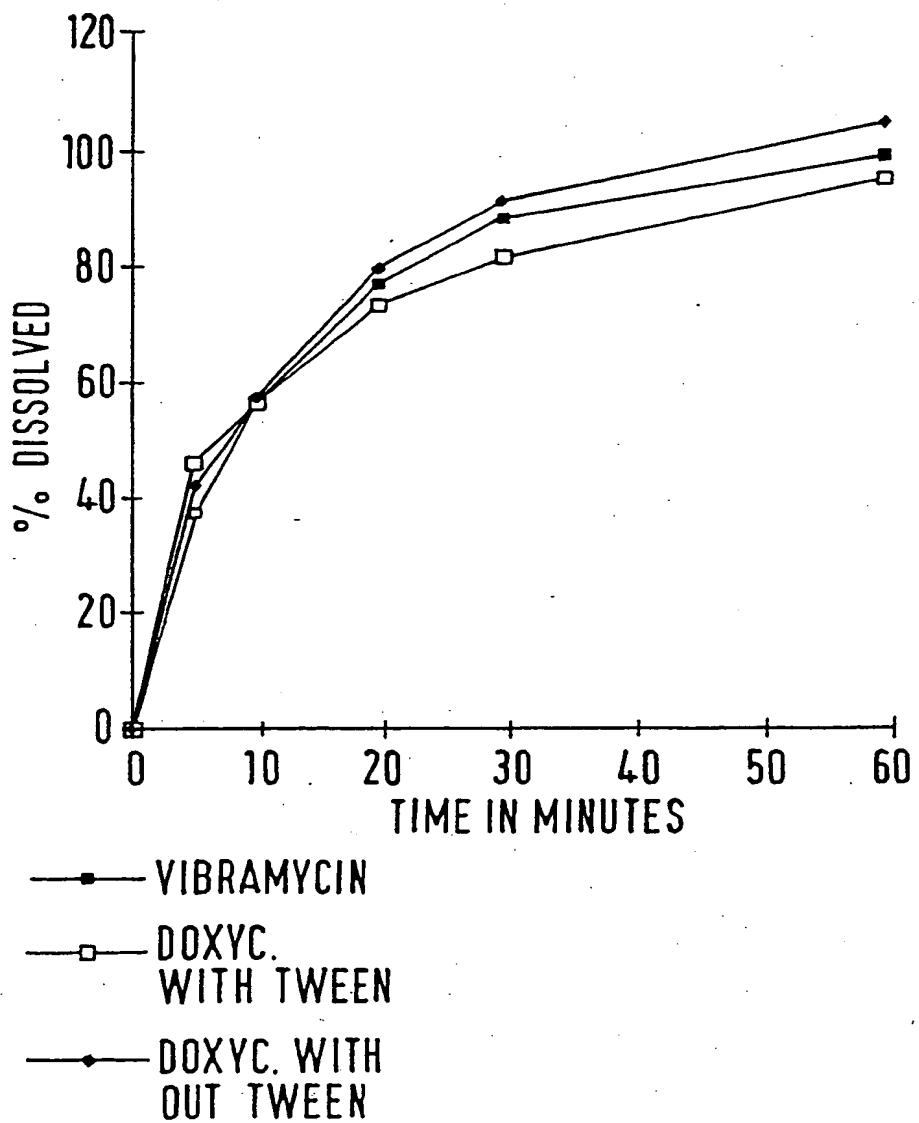
23. A method of treatment of a warm-blooded animal with an effective amount of a biologically active organic compound to combat a condition responsive to said compound, characterized in that said compound is administered as a salt with a sugar acid, with the proviso that said salt is other than a sucrose-octa-O-sulphonic acid salt of an aminoglycoside.

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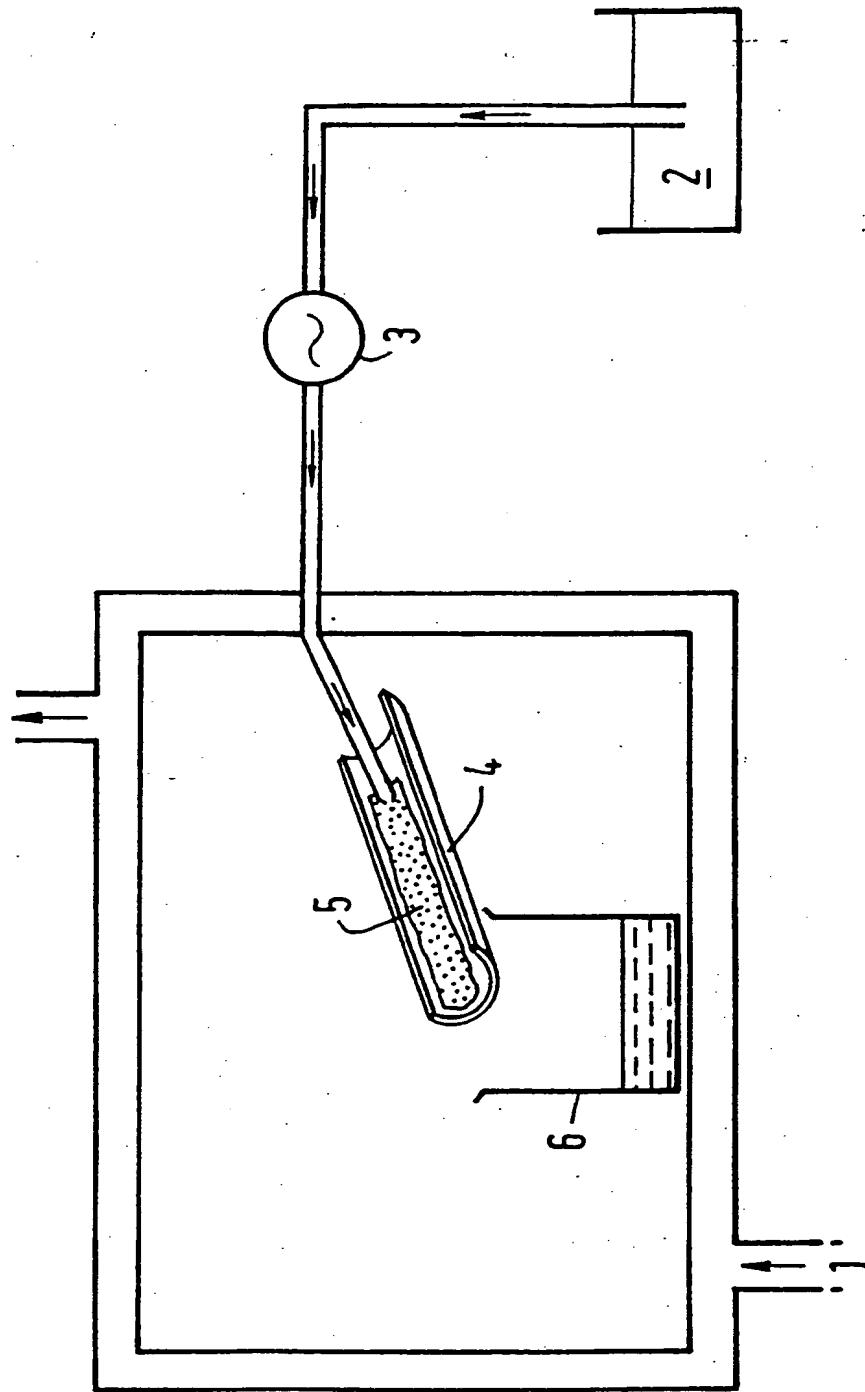
24. A method as claimed in claim 23 wherein said salt is administered perorally.

25. A method as claimed in claim 23 wherein said salt is administered topically to a mucous membrane.

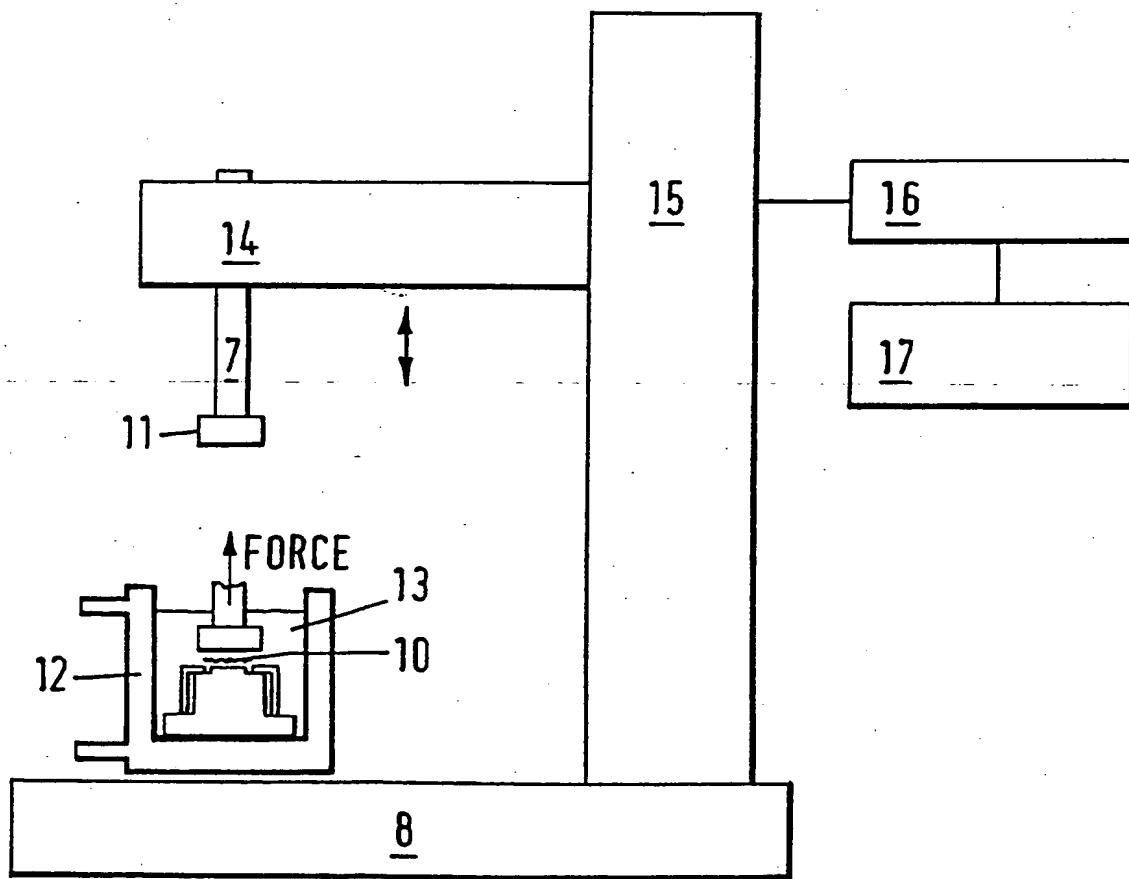
1/3



2/3



3/3





INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6: C07H 11/00, 11/04, A61K 31/70, 31/715, 31/66, 47/48, C07F 9/117, C08L 5/02, C07K 7/58, 7/62, C07H 15/22, 15/234, 17/08		A3	(11) International Publication Number: WO 95/34571 (43) International Publication Date: 21 December 1995 (21.12.95)
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(74) Agents: COCKBAIN, Julian et al.; Frank B. Dehn & Co., Imperial House, 15-19 Kingsway, London WC2B 6UZ (GB).			
(54) Title: DRUG SALTS			
(57) Abstract It has been found that sugar acid salts represent beneficial controlled release forms for basic organic drug compounds. Examples of appropriate salts include mono, di, oligo and polysaccharide poly-O-sulphonic acid salts of antibiotics such as tetracyclines.			

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 95/02254

A. CLASSIFICATION OF SUBJECT MATTER				
IPC 6	C07H11/00	C07H11/04	A61K31/70	A61K31/715
	A61K47/48	C07F9/117	C08L5/02	C07K7/58
	C07H15/22	C07H15/234	C07H17/08	C07K7/62

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D C07F C07H A61K C07K C08L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 211 268 (ZAPPIA V.) 25 February 1987 see column 4, line 40 - column 7, line 35; claims; example 8 ---	1,22-25
X	GB,A,1 227 830 (SOCIETE GENERALE DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES) 7 April 1971 see the whole document ---	1,22-25
P,X	WO,A,95 07914 (A/S DUMEX) 23 March 1995 see the whole document -----	1,22-25

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

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- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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- *&* document member of the same patent family

Date of the actual completion of the international search

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Date of mailing of the international search report

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Day, G

INTERNATIONAL SEARCH REPORT

International application No.?

PCT/EP 95/02254

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 23-25

because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 23-25 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. Claims Nos.:

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. Claims: 1-4,6-16,19,21-25 (in part); 5,17,20 (complete)
2. Claims: 1-3,6-16,18,19,21-25 (all in part)
3. Claims: 1,2,6-16,19,21-25 (all in part)
4. Claims: 1,2,6-16,19,21-25 (all in part)
5. Claims: 1-4,6-16,18-25 (all in part).

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

1-4,6-16,18-25
(in part); and
5,17,20 (complete)

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 95/02254

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-211268	25-02-87	DE-A-	3681529	24-10-91
		JP-A-	62036367	17-02-87
GB-A-1227830	07-04-71	BE-A-	735129	01-12-69
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		DE-A-	1936723	14-05-70
		FR-A-	2013170	27-03-70
		NL-A-	6910987	20-01-70
		DA-A-	3630	24-12-71
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